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<b>(30) Priority Data:</b> <table><tr><td>60/045,838</td><td>7 May 1997 (07.05.97)</td><td>US</td></tr><tr><td>60/046,868</td><td>8 May 1997 (08.05.97)</td><td>US</td></tr><tr><td>60/049,324</td><td>11 June 1997 (11.06.97)</td><td>US</td></tr><tr><td>60/050,413</td><td>20 June 1997 (20.06.97)</td><td>US</td></tr><tr><td>60/050,412</td><td>20 June 1997 (20.06.97)</td><td>US</td></tr><tr><td>60/050,977</td><td>20 June 1997 (20.06.97)</td><td>US</td></tr><tr><td>60/059,381</td><td>19 September 1997 (19.09.97)</td><td>US</td></tr><tr><td>60/059,384</td><td>19 September 1997 (19.09.97)</td><td>US</td></tr><tr><td>60/059,336</td><td>19 September 1997 (19.09.97)</td><td>US</td></tr><tr><td>60/059,544</td><td>19 September 1997 (19.09.97)</td><td>US</td></tr><tr><td>60/059,677</td><td>19 September 1997 (19.09.97)</td><td>US</td></tr><tr><td>60/059,971</td><td>25 September 1997 (25.09.97)</td><td>US</td></tr><tr><td>60/060,194</td><td>26 September 1997 (26.09.97)</td><td>US</td></tr></table>			60/045,838	7 May 1997 (07.05.97)	US	60/046,868	8 May 1997 (08.05.97)	US	60/049,324	11 June 1997 (11.06.97)	US	60/050,413	20 June 1997 (20.06.97)	US	60/050,412	20 June 1997 (20.06.97)	US	60/050,977	20 June 1997 (20.06.97)	US	60/059,381	19 September 1997 (19.09.97)	US	60/059,384	19 September 1997 (19.09.97)	US	60/059,336	19 September 1997 (19.09.97)	US	60/059,544	19 September 1997 (19.09.97)	US	60/059,677	19 September 1997 (19.09.97)	US	60/059,971	25 September 1997 (25.09.97)	US	60/060,194	26 September 1997 (26.09.97)	US	<b>(74) Agents:</b> ROSE, Bernard, F. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).
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<b>(54) Title:</b> 2-INDOLINONE DERIVATIVES AS MODULATORS OF PROTEIN KINASE ACTIVITY																																										
<b>(57) Abstract</b> <p>The present invention relates to novel 2-indolinones and physiologically acceptable salts and prodrugs thereof which modulate the activity of protein kinases and therefore are expected to be useful in the prevention and treatment of protein kinase related cellular disorders such as cancer.</p>																																										

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DESCRIPTION2-Indolinone Derivatives as Modulators  
of Protein Kinase ActivityIntroduction

5       The present invention relates generally to organic chemistry, biochemistry, pharmacology and medicine. More particularly, it relates to novel 2-indolinone derivatives and their physiologically acceptable salts and prodrugs which modulate the activity of protein kinases ("PKs") and, 10 therefore, are expected to exhibit a salutary effect against disorders related to abnormal PK activity.

Background Of The Invention

15       The following is offered as background information only and is not admitted to be prior art to the present invention.

      PKs are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell growth, differentiation and proliferation; i.e., virtually all aspects of cell life in one way or 20 another depend on PK activity. Furthermore, abnormal PK activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as 25 glioblastoma (brain cancer).

      The PKs can conveniently be broken down into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs).

30       One of the prime aspects of PTK activity is its involvement with growth factor receptors. Growth factor

receptors are cell-surface proteins. When bound by a growth factor ligand, growth factor receptors are converted to an active form which interacts with proteins on the inner surface of a cell membrane. This leads to phosphorylation on tyrosine residues of the receptor and other proteins and to the formation inside the cell of complexes with a variety of cytoplasmic signaling molecules that, in turn, affect numerous cellular responses such as cell division (proliferation), cell differentiation, cell growth, expression of metabolic effects to the extracellular microenvironment, etc. For a more complete discussion, see Schlessinger and Ullrich, Neuron, 9:303-391 (1992) which is incorporated by reference, including any drawings, as if fully set forth herein.

Growth factor receptors with PK activity are known as receptor tyrosine kinases ("RTKs"). They comprise a large family of transmembrane receptors with diverse biological activity. At present, at least nineteen (19) distinct subfamilies of RTKs have been identified. An example of these is the subfamily designated the "HER" RTKs, which include EGFR (epithelial growth factor receptor), HER2, HER3 and HER4. These RTKs consist of an extracellular glycosylated ligand binding domain, a transmembrane domain and an intracellular cytoplasmic catalytic domain that can phosphorylate tyrosine residues on proteins.

Another RTK subfamily consists of insulin receptor (IR), insulin-like growth factor I receptor (IGF-1R) and the insulin receptor related receptor (IRR). IR and IGF-1R interact with insulin, IGF-I and IGF-II to form a heterotetramer of two entirely extracellular glycosylated  $\alpha$  subunits and two  $\beta$  subunits which cross the cell membrane and which contain the tyrosine kinase domain.



A third RTK subfamily is referred to as the platelet derived growth factor receptor ("PDGFR") group, which includes PDGFR $\alpha$ , PDGFR $\beta$ , CSFIR, c-kit and c-fms. These receptors consist of glycosylated extracellular domains composed of variable numbers of immunoglobulin-like loops and an intracellular domain wherein the tyrosine kinase domains is interrupted by unrelated amino acid sequences.

Another group which, because of its similarity to the PDGFR subfamily, is sometimes subsumed in the later group is the fetus liver kinase ("flk") receptor subfamily. This group is believed to be made of up of kinase insert domain-receptor fetal liver kinase-1 (KDR/FLK-1), flk-1R, flk-4 and fms-like tyrosine kinase 1 (flt-1).

One further member of the tyrosine kinase growth factor receptor family is the fibroblast growth factor ("FGF") receptor group. This groups consists of four receptors, FGFR1-4, and seven ligands, FGF1-7. While not yet well defined, it appears that the receptors consist of a glycosylated extracellular domain containing a variable number of immunoglobulin-like loops and an intracellular domain in which the PTK sequence is interrupted by regions of unrelated amino acid sequences.

A more complete listing of the known RTK subfamilies is described in Plowman et al., DN&P, 7(6):334-339 (1994) which is incorporated by reference, including any drawings, as if fully set forth herein.

In addition to the RTKs, there also exists a family of entirely intracellular PTKs called "non-receptor tyrosine kinases" or "cellular tyrosine kinases". This latter designation, abbreviated "CTK", will be used herein. CTKs do not contain extracellular and transmembrane domains. At present, over 24 CTKs in 11 subfamilies (Src, Frk, Btk, Csk,

Abl, Zap70, Fes/Fps, Fak, Jak and Ack) have been identified. The Src subfamily appear so far to be the largest group of CTKs and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. For a more detailed discussion of CTKs, see Bolen,  
5 Oncogene, 8:2025-2031 (1993), which is incorporated by reference, including any drawings, as if fully set forth herein.

The serine-threonine kinases or STKs, like the CTKs, are predominantly intracellular although there are a few  
10 receptor kinases of the STK type. STKs are the most common of the cytosolic kinases; i.e., kinases which perform their function in that part of the cytoplasm other than the cytoplasmic organelles and cytoskelton. The cytosol is the region within the cell where much of the cell's intermediary  
15 metabolic and biosynthetic activity occurs; e.g., it is in the cytosol that proteins are synthesized on ribosomes.

RTKs, CTKs and STKs have all been implicated in a host of pathogenic conditions including, significantly, large number of diverse cancers. Others pathogenic conditions  
20 which have been associated with PTKs include, without limitation, psoriasis, hepatic cirrhosis, diabetes, atherosclerosis, angiogenesis, restinosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders, autoimmune disease and a variety of renal disorders.

25 With regard to cancer, two of the major hypotheses advanced to explain the excessive cellular proliferation that drives tumor development relate to functions known to be PK regulated. That is, it has been suggested that malignant cell growth results from a breakdown in the  
30 mechanisms that control cell division and/or differentiation. It has been shown that the protein products of a number of proto-oncogenes are involved in the signal

transduction pathways that regulate cell growth and differentiation. These protein products of proto-oncogenes include the extracellular growth factors, transmembrane growth factor PTK receptors (RTKs), cytoplasmic PTKs (CTKs) and cytosolic STKs, discussed above.

In view of the apparent link between PK-related cellular activities and a number of human disorders, it is no surprise that a great deal of effort is being expended in an attempt to identify ways to modulate PK activity. Some of these have involved biomimetic approaches using large molecules patterned on those involved in the actual cellular processes (e.g., mutant ligands (U.S. App. No. 4,966,849); soluble receptors and antibodies (App. No. WO 94/10202, Kendall and Thomas, Proc. Nat'l Acad. Sci., 90:10705-09 (1994), Kim, et al., Nature, 362:841-844 (1993)); RNA ligands (Jelinek, et al., Biochemistry, 33:10450-56); Takano, et al., Mol. Bio. Cell 4:358A (1993); Kinsella, et al., Exp. Cell Res. 199:56-62 (1992); Wright, et al., J. Cellular Phys., 152:448-57) and tyrosine kinase inhibitors (WO 94/03427; WO 92/21660; WO 91/15495; WO 94/14808; U.S. Pat. No. 5,330,992; Mariani, et al., Proc. Am. Assoc. Cancer Res., 35:2268 (1994)).

More recently, attempts have been made to identify small molecules which act as PK inhibitors. For example, bis- monocyclic, bicyclic and heterocyclic aryl compounds (PCT WO 92/20642), vinylene-azaindole derivatives (PCT WO 94/14808) and 1-cyclopropyl-4-pyridylquinolones (U.S. Pat. No. 5,330,992) have been described as PTK inhibitors. Styryl compounds (U.S. Pat. No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Pat. No. 5,302,606), quinazoline derivatives (EP App. No. 0 566 266 A1), selenaindoles and selenides (PCT WO 94/03427), tricyclic

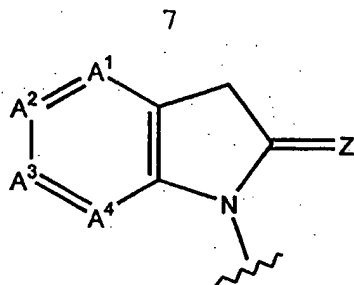
polyhydroxylic compounds (PCT WO 92/21660) and benzylphosphonic acid compounds (PCT WO 91/15495) have all been described as PTK inhibitors useful in the treatment of cancer.

5 Our own efforts to identify small organic molecules which modulate PK activity and which, therefore, should be useful in the treatment and prevention of disorders driven by abnormal PK activity, has led us to the discovery of a family of novel 2-indolinone derivatives which exhibit  
10 excellent PK modulating ability and which are the subject of this invention.

#### Summary Of The Invention

The present invention relates generally to novel 2-indolinone derivatives and their salts and prodrugs which  
15 modulate the activity of receptor protein tyrosine kinases (RTK), non-receptor protein tyrosine kinases (CTK) and serine/threonine protein kinases (STK). In addition, the present invention relates to the preparation and use of pharmacological compositions of the disclosed compounds and  
20 their physiologically acceptable salts and prodrugs in the treatment or prevention of PK driven disorders such as, by way of example and not limitation, cancer, diabetes, hepatic cirrhosis, atherosclerosis, angiogenesis and renal disease.

The terms "2-indolinone" and "2-oxindole" are used  
25 interchangeably herein; both refer to a chemical compound having the general structure:



wherein A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> and A<sup>4</sup> are carbon and Z is oxygen. It is to be understood, however, that this invention also features compounds wherein Z is sulfur and/or A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> and/or A<sup>4</sup> are nitrogen; thus, wherever the terms "2-indolinone" or "2-oxindole" are used herein, they are to be construed as including the sulfur and nitrogen analogs as well.

A "pharmacological composition" refers to a mixture of one or more of the compounds described herein, or physiologically acceptable salts thereof, with other chemical components, such as physiologically acceptable carriers and/or excipients. The purpose of a pharmacological composition is to facilitate administration of a compound to an organism.

As used herein, a "physiologically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

An "excipient" refers to an inert substance added to a pharmacological composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

A "prodrug" refers to an agent which is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by

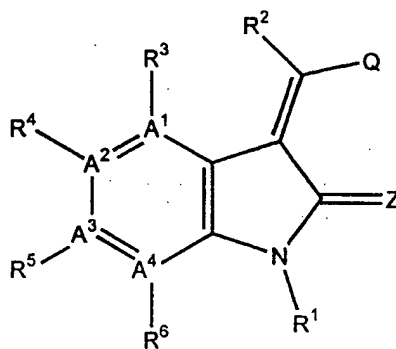
oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmacological compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water solubility is beneficial.

As used herein, an "ester" is a carboxy group, as defined herein, wherein R" is any of the listed groups other than hydrogen.

### 1. The Compounds

#### 15 General Structural Features.

In one aspect the present invention features compounds having the general chemical structure:



1

20 Physiologically acceptable salts and prodrugs of the featured compounds as well as pharmacological compositions

of the compounds, salts and prodrugs are within the scope of this invention.

A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> and A<sup>4</sup>, are independently selected from the group consisting of carbon and nitrogen, it being understood  
5 that the 9-member bicyclic ring formed is one known in the chemical arts; it further being understood that, when A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> or A<sup>4</sup> is nitrogen, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup>, respectively, does not exist.

R<sup>1</sup> is selected from the group consisting of hydrogen,  
10 alkyl, cycloalkyl, alkenyl, alkynyl, aryl, hydroxy, alkoxy, carbonyl, C-carboxy, O-carboxy, C-amido, C-thioamido, guanyl, guanadino, ureido, sulfonyl and trihalomethane-sulfonyl.

R<sup>2</sup> is selected from the group consisting of hydrogen,  
15 alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic and halo.

R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, alkyl, trihalomethyl, cyclo-  
alkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic,  
20 hydroxy, thiohydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, N-trihalomethanesulfonamido, carbonyl, trihalomethylcarbonyl, C-carboxy, O-carboxy, cyano, nitro, halo, cyanato, isocyanato, thiocyanato, isothiocyanato, O-  
25 carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, phosphonyl, guanyl, guanidino, ureido, C-amido, N-amido, amino, -NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>C(=Y)T, -N=CNR<sup>18</sup>R<sup>19</sup>, -NHR<sup>20</sup> and -(alk<sub>1</sub>)<sub>r</sub>M.

R<sup>18</sup> and R<sup>19</sup> are independently selected from the group  
30 consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, trihalomethylcarbonyl, C-carboxy, trihalomethanesulfonyl,

sulfonyl, C-peptidyl and, combined, a five-member or a six-member heteroalicyclic ring.

W is selected from the group consisting of nitrogen, oxygen and sulfur.

5 The (alk<sub>1</sub>) group is selected from the group consisting of optionally substituted alkyl  $-(CRR')-$ , optionally substituted ethylene  $-(CR=CR')-$  and acetylene  $-(C\equiv C)-$ .

R and R' are independently selected from the groups consisting of hydrogen, alkyl, cycloalkyl, aryl, alkoxy, 10 thioalkoxy, aryloxy and halo.

With regard to r, it can be 1 to 10, inclusive.

M is a polar group.

T is selected from the group consisting of hydroxy, alkoxy, aryloxy, amino, N-hydroxylamino, O-carboxy,  $-NR^{18}R^{19}$  15 and  $-N$ -peptidyl.

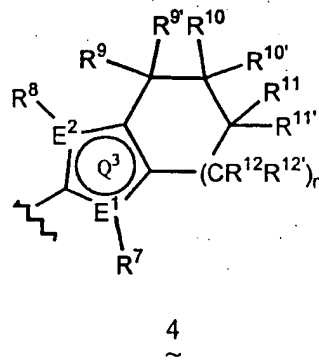
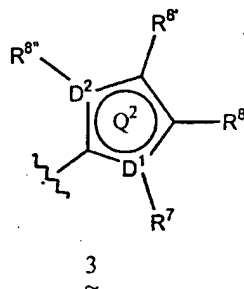
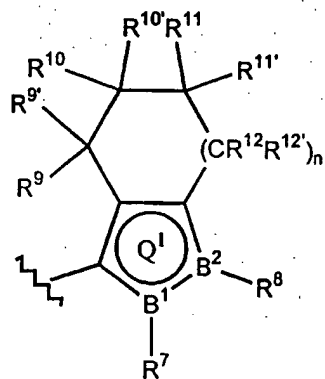
As for m, it can be 0, 1, 2 or 3.

Y is selected from the group consisting of oxygen and sulfur.

$R^{20}$  is a polyhydroxyalkyl group.

20  $R^3$  and  $R^4$  or  $R^4$  and  $R^5$  or  $R^5$  and  $R^6$  may combine to form a methylenedioxy or an ethylenedioxy group.

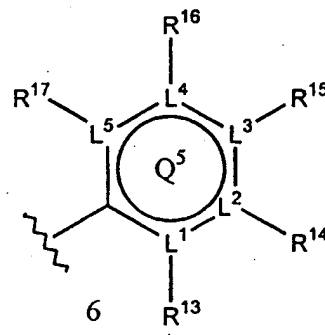
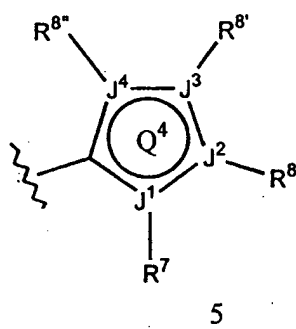
Q is selected from the group consisting:





B<sup>1</sup> and B<sup>2</sup> are selected from the group consisting of carbon, nitrogen, oxygen and sulfur such that 5-member heteroaryl ring Q<sup>1</sup> is one known in the chemical arts.

- 5 R<sup>7</sup>, R<sup>8</sup>, R<sup>8'</sup>, R<sup>8''</sup>, R<sup>9</sup>, R<sup>9'</sup>, R<sup>10</sup>, R<sup>10'</sup>, R<sup>11</sup>, R<sup>11'</sup>, R<sup>12</sup> and R<sup>12'</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are independently selected from the group consisting of hydrogen, alkyl, trihalomethyl, cycloalkyl, trihalomethylcarbonyl, alkenyl, alkynyl, aryl,



- heteroaryl, heteroalicyclic, alkoxy, aryloxy, thioalkoxy, thioaryloxy, heteroaryloxy, heteroalicycloxy, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, carbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, phosphonyl, guanyl, guanidino, ureido, trihalomethanesulfonyl, trihalo-
- 15 methanesulfonamido, amino, -NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>C(=Y)T, -N=CNR<sup>18</sup>R<sup>19</sup>, -NHR<sup>20</sup> and -(alk<sub>1</sub>)<sub>r</sub>M.

- R<sup>7</sup> and R<sup>8</sup>, R<sup>8</sup> and R<sup>8'</sup> or R<sup>8'</sup> and R<sup>8''</sup>, combined, may form a five-member cycloalkyl, heteroaryl or heteroalicyclic ring or a six-member cycloalkyl, aryl, heteroaryl or hetero-
- 20 alicyclic ring.

R<sup>7</sup> and R<sup>8</sup> and, when R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> or R<sup>12</sup> is hydrogen, R<sup>9'</sup>, R<sup>10'</sup>, R<sup>11'</sup> or R<sup>12'</sup>, respectively, in addition to being selected from the above groups, may also be independently selected from the group consisting of hydroxy and thiohydroxy.

Furthermore,  $R^9$  and  $R^{9'}$ ,  $R^{10}$  and  $R^{10'}$ ,  $R^{11}$  and  $R^{11'}$  or  $R^{12}$  and  $R^{12'}$ , combined, may form a keto, five-member spirocycloalkyl, five-member spiroheteroalicyclic, six-member spirocycloalkyl or six-member spiroheteroalicyclic group.

5         $D^1$  is selected from the group consisting of carbon and nitrogen.

$D^2$  is selected from the group consisting of nitrogen, oxygen and sulfur.

It is understood that, when  $D^1$  is nitrogen and  $D^2$  is  
10        oxygen or sulfur,  $R^7$  does not exist.

$E^1$  is selected from the group consisting of carbon and nitrogen.

$E^2$  is selected from the group consisting of nitrogen, oxygen and sulfur.

15        It is understood that, when  $E^1$  is nitrogen and  $E^2$  is oxygen or sulfur,  $R^8$  does not exist.

$J^1$  is selected from the group consisting of oxygen, nitrogen and sulfur.

$J^2$ ,  $J^3$  and  $J^4$  are independently selected from the group  
20        consisting of carbon, nitrogen, oxygen and sulfur, such that the five-member heteroaryl ring  $Q^4$  is one known in the chemical arts. It is to be further understood that, when  $J^2$ ,  $J^3$  or  $J^4$  is nitrogen, oxygen or sulfur,  $R^8$ ,  $R^{8'}$  or  $R^{8''}$ , respectively, do not exist; likewise when  $J^1$  is oxygen or  
25        sulfur,  $R^7$  does not exist.

$L^1$ ,  $L^2$ ,  $L^3$ ,  $L^4$  and  $L^5$  are independently selected from the group consisting of carbon and nitrogen such that any 6-member nitrogen-containing heteroaryl ring  $Q^5$  formed is one known in the chemical arts and that, when  $L^1$ ,  $L^2$ ,  $L^3$ ,  $L^4$  or  $L^5$   
30        is nitrogen  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  or  $R^{17}$ , respectively, do not exist.

As used herein, the term "alkyl" refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; e.g., "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, C-carboxy, O-carboxy, cyanato, isocyanato, thiocyanato, sothiocyanato, nitro, silyl, amino and  $-NR^{18}R^{19}$ ,  $R^{18}$  and  $R^{19}$  being defined above.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share an adjacent pair of carbon atoms) group wherein one of more of the rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, adamantane, cyclohexadiene, cycloheptane and, cycloheptatriene. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, halo, carbonyl, thiocarbonyl, carboxy, O-carbamyl, N-carbamyl, C-amido, N-

amido, nitro, amino and  $-NR^{18}R^{19}$ , with  $R^{18}$  and  $R^{19}$  being defined above.

An "alkenyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least  
5 one carbon-carbon double bond.

An "alkynyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond.

An "aryl" group refers to an all-carbon monocyclic or  
10 fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted,  
15 tuted, the substituted group(s) is preferably one or more selected from halo, trihalomethyl, alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, O-carbamyl, N-carbamyl, O-thio-  
20 carbamyl, N-thiocarbamyl, C-amido, N-amido, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethane-sulfonamido, amino and  $-NR^{18}R^{19}$ ,  $R^{18}$  and  $R^{19}$  being defined above.

As used herein, a "heteroaryl" group refers to a  
25 monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Examples, without limita-  
30 tion, of heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline, purine and carbazole. The

heteroaryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, halo, trihalomethyl, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, carbonyl, thiocarbonyl, sulfonamido, carboxy, sulfinyl, sulfonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, amino and  $-NR^{18}R^{19}$ ,  $R^{18}$  and  $R^{19}$  being defined above.

A "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are piperidine, morpholine, piperazine, pyrrolidine, dihydrothiophene, tetrahydrofuran, etc. The heteroalicyclic ring may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, halo, trihalomethyl, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, carbonyl, thiocarbonyl, carboxy, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, sulfinyl, sulfonyl, C-amido, N-amido, amino and  $-NR^{18}R^{19}$ ,  $R^{18}$  and  $R^{19}$  as defined above.

A "hydroxy" group refers to an -OH group.

An "alkoxy" group refers to both an -O-alkyl and an -O-cycloalkyl group, as defined herein.

An "aryloxy" group refers to both an -O-aryl and an -O-heteroaryl group, as defined herein.

A "heteroalicycloxy" group refers to an -O-heteroalicyclic group.

A "thiohydroxy" group refers to an -SH group.

A "thioalkoxy" group refers to both an S-alkyl and an -S-cycloalkyl group, as defined herein.

A "thioaryloxy" group refers to both an -S-aryl and an -S-heteroaryl group, as defined herein.

5       A "carbonyl" group refers to a  $-C(=O)-R''$  group, where  $R''$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as defined herein.

10       A "trihalomethylcarbonyl" group refers to a  $X_3CC(=O)-$  group wherein X is a halo group as defined herein.

An "aldehyde" group refers to a carbonyl group where  $R''$  is hydrogen.

15       A "thiocarbonyl" group refers to a  $-C(=S)-R''$  group, with  $R''$  as defined herein.

An "O-carboxy" group refers to a  $R''C(=O)O-$  group, with  $R''$  as defined herein.

A "C-carboxy" group refers to a  $-C(=O)OR''$  groups with  $R''$  as defined herein.

20       An "acetyl" group refers to a  $-C(=O)CH_3$  group.

A "carboxyalkyl" group refers to  $-(CH_2)_sC(O)OR''$  wherein s is 1-6 and  $R''$  is as defined above.

A "carboxylic acid" group refers to a C-carboxy group in which  $R''$  is hydrogen.

25       A "halo" group refers to fluorine, chlorine, bromine or iodine.

A "trihalomethyl" group refers to a  $-CX_3$  group wherein X is a halo group as defined herein.

30       A "trihalomethanesulfonyl" group refers to a  $X_3CS(=O)_2-$  groups with X as defined above.

A "cyano" group refers to a  $-C\equiv N$  group.

A "cyanato" group refers to a  $-CNO$  group.

An "isocyanato" group refers to a -NCO group.

A "thiocyanato" group refers to a -CNS group.

An "isothiocyanato" group refers to a -NCS group.

5 A "sulfinyl" group refers to a -S(=O)-R" group, with R" as defined herein.

A "sulfonyl" group refers to a -S(=O)<sub>2</sub>R" group, with R" as defined herein.

A "sulfonamido" group refers to a -S(=O)<sub>2</sub>-NR<sup>18</sup>R<sup>19</sup>, with R<sup>18</sup> and R<sup>19</sup> as defined herein.

10 A "trihalomethanesulfonamido" group refers to a X<sub>3</sub>CS(=O)<sub>2</sub>N(R<sup>18</sup>)- group with X and R<sup>18</sup> as defined herein.

An "O-carbamyl" group refers to a -OC(=O)NR<sup>18</sup>R<sup>19</sup> group with R<sup>18</sup> and R<sup>19</sup> as defined herein.

15 An "N-carbamyl" group refers to a R<sup>19</sup>OC(=O)NR<sup>18</sup>- group, with R<sup>18</sup> and R<sup>19</sup> as defined herein.

An "O-thiocarbamyl" group refers to a -OC(=S)-NR<sup>18</sup>R<sup>19</sup> group with R<sup>18</sup> and R<sup>19</sup> as defined herein.

An "N-thiocarbamyl" group refers to an R<sup>19</sup>OC(=S)NR<sup>18</sup>- group, with R<sup>18</sup> and R<sup>19</sup> as defined herein.

20 An "amino" group refers to an -NR<sup>18</sup>R<sup>19</sup> group, with R<sup>18</sup> and R<sup>19</sup> both being hydrogen.

A "quaternary ammonium" group refers to a -<sup>+</sup>NR<sup>18</sup>R<sup>18'</sup>R<sup>19</sup> with R<sup>18</sup> and R<sup>19</sup> as defined herein and R<sup>18'</sup> defined the same as R<sup>18</sup> and R<sup>19</sup>.

25 A "C-amido" group refers to a -C(=O)-NR<sup>18</sup>R<sup>19</sup> group with R<sup>18</sup> and R<sup>19</sup> as defined herein.

An "N-amido" group refers to an R<sup>18</sup>C(=O)NR<sup>19</sup>- group, with R<sup>18</sup> and R<sup>19</sup> as defined herein.

30 A "C-thioamido" group refers to a -C(=S)NR<sup>18</sup>R<sup>19</sup> group, with R<sup>18</sup> and R<sup>19</sup> as defined herein.

A "nitro" group refers to a -NO<sub>2</sub> group.

A "methylenedioxy" group refers to a  $-OCH_2O-$  group wherein the oxygen atoms are bonded to adjacent ring carbon atoms.

5 An "ethylenedioxy" group refers to a  $-OCH_2CH_2O-$  group wherein the oxygen atoms are bonded to adjacent ring carbon atoms.

A "guanyl" group refers to an  $R^{18}R^{19}NC(=N)-$  group with  $R^{18}$  and  $R^{19}$  as defined herein.

10 A "guanadiny" group refers to an  $-R^{18}NC(=N)NR^{18'}R^{19}$  group with  $R^{18}$  and  $R^{19}$  as defined herein,  $R^{18'}$  being defined the same as  $R^{18}$  and  $R^{19}$ .

A "ureidyl" group refers to an  $-NR^{18}C(=O)NR^{18'}R^{19}$  group with  $R^{18}$  and  $R^{19}$  as defined herein and  $R^{18'}$  defined the same as  $R^{18}$  and  $R^{19}$ .

15 A "phosphonyl" group refers to an  $-OP(=O)_2OR''$  group with  $R''$  as defined herein.

A "C-peptidyl" group refers to a group formed by the reaction of the 2-amino group of an amino acid with the carboxy group of another amino acid; i.e., a peptidyl group  
20 has the general structure  $-(NCHRC(=O))_n-$  where the R group can be the same or different depending on which amino acid is used to make the peptidyl group, the "C-peptidyl" designation referring to the situation where the peptidyl group is bonded to a non-amino acid molecule through the  
25  $C(=O)$  carbon.

A "polar group" refers to a group wherein the nuclei of the atoms covalently bound to each other to form the group do not share the electrons of the covalent bond(s) joining them equally; that is the electron cloud is denser about one  
30 atom than another. This results in one end of the covalent bond(s) being relatively negative and the other end relatively positive; i.e., there is a negative pole and a



positive pole. Examples of polar groups include, without limitation, hydroxy, alkoxy, carboxy, nitro, cyano, amino, quaternary ammonium, amido, ureidyl, sulfonamido, sulfinyl, sulfonyl, phosphono, morpholino, piperazinyl and tetrazolyl.

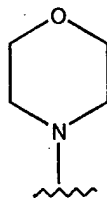
- 5 A "spirocycloalkyl" group refers to cycloalkyl group which shares a ring carbon atom with another ring.

A "spiroheteroalicyclic" group refers to a heteroalicyclic group which shares a ring carbon atom with another ring.

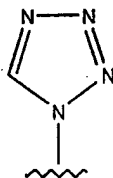
- 10 An "N-hydroxylamino" group refers to a  $R''\text{ONR}^{18}$ - group with  $R''$  and  $R^{18}$  as defined herein.

- A "polyhydroxyalkyl" group refers to a 1 to 8 carbon, preferably a 1 to 4 carbon unbranched alkyl group substituted with 2 or more, preferably 3 or more hydroxyl  
15 groups only.

A "morpholinyl" group refers to a group having the chemical structure:

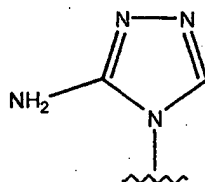


- A "tetrazolyl" group refers to a group having the  
20 chemical structure:

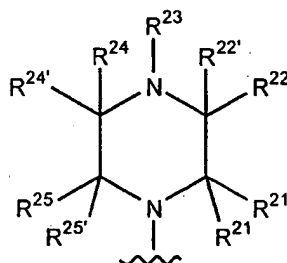


An "aminotriazolyl" group refers to a group having the chemical structure:

20



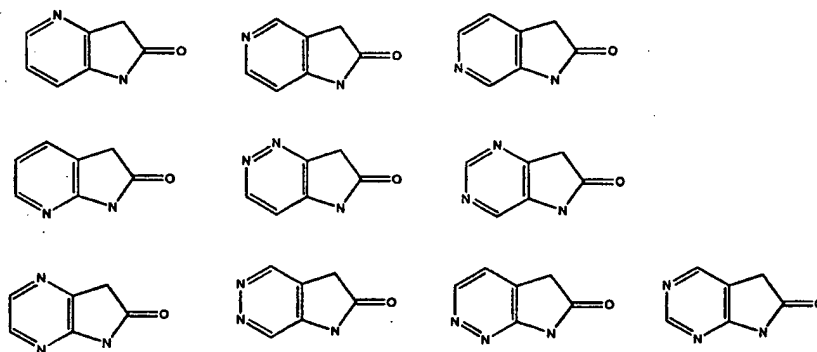
A "1-piperazinyl" group refers to a group having the chemical structure:



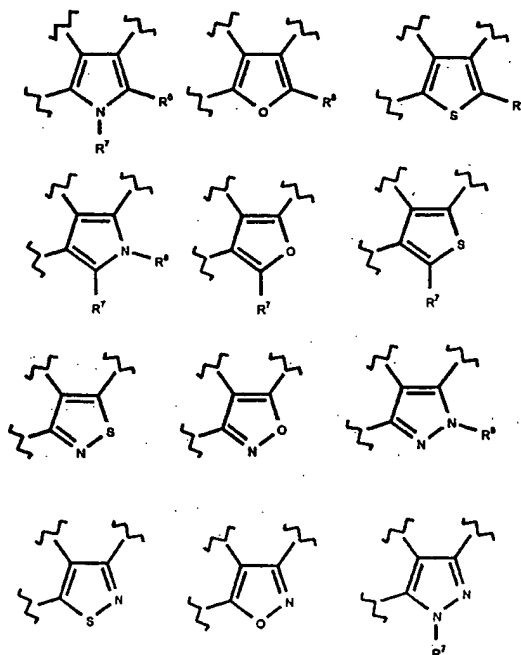
5

wherein  $R^{21}$ ,  $R^{21'}$ ,  $R^{22}$ ,  $R^{22'}$ ,  $R^{23}$ ,  $R^{23'}$ ,  $R^{24}$ ,  $R^{24'}$ ,  $R^{25}$  and  $R^{25'}$  are independently selected from the group consisting of hydrogen, unsubstituted lower alkyl, trihalomethyl, unsubstituted cycloalkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted heteroalicyclic, hydroxy, unsubstituted lower alkyl alkoxy, unsubstituted aryloxy, thiohydroxy, unsubstituted lower alkyl thioalkoxy, unsubstituted thioaryloxy, sulfinyl substituted with unsubstituted lower alkyl, sulfonyl substituted with hydrogen or unsubstituted lower alkyl, N-sulfonamido, S-sulfonamido, carbonyl substituted with hydrogen or unsubstituted lower alkyl, trihalomethyl-carbonyl, C-carboxy substituted with hydrogen or unsubstituted lower alkyl, O-carboxy substituted with unsubstituted lower alkyl, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, amino and  $-NR^{18}R^{19}$ ,  $R^{18}$  and  $R^{19}$  being independently selected from the group consisting of hydrogen and unsubstituted lower alkyl.

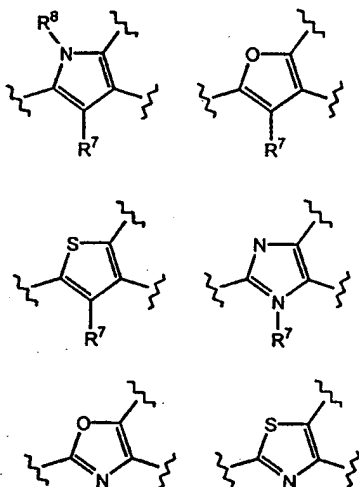
By way of example and not limitation, 9-member bicyclic rings known in the chemical arts include the following:



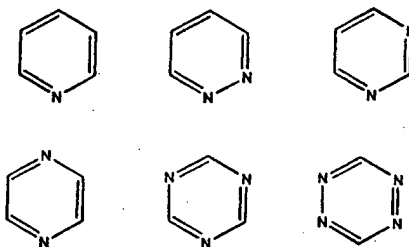
By way of further example and, likewise, not limitation, 5-member heteroaryl rings  $Q^1$  known in the chemical arts include the following:



Similarly, non-limiting examples of 5-member heteroaryl rings  $Q^4$  known in the chemical arts include the following:



Finally, non-limiting examples of nitrogen-containing 6-member heteroaryl rings  $Q^5$  known in the chemical arts include the following:



#### B. Preferred Structural Features.

10 A preferred structural feature of the compounds of this invention is that Z is oxygen.

Likewise, in preferred features of this invention,  $R^1$  and  $R^2$  and  $R^7$  are hydrogen.

Another preferred feature of this invention is that  $A^1$ ,  
 15  $A^2$ ,  $A^3$  and  $A^4$  are carbon.

It is also a preferred feature of this invention that A<sup>1</sup> or A<sup>2</sup> or A<sup>3</sup> or A<sup>4</sup> is nitrogen while the remaining positions in the heteroaromatic ring thus formed are carbon.

It is likewise preferred that A<sup>2</sup> and A<sup>4</sup> are nitrogen  
5 while A<sup>1</sup> and A<sup>3</sup> are carbon.

In another preferred feature of this invention, in the same molecule, Z is oxygen, R<sup>1</sup>, R<sup>2</sup> and R<sup>7</sup> are hydrogen and A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> and A<sup>4</sup> are carbon.

It is a preferred feature of this invention that one of  
10 A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> or A<sup>4</sup> is nitrogen, Z is oxygen and R<sup>1</sup>, R<sup>2</sup> and R<sup>7</sup> are hydrogen.

In other preferred features of this invention, A<sup>1</sup> and A<sup>3</sup> are carbon, A<sup>2</sup> and A<sup>4</sup> are nitrogen, Z is oxygen and R<sup>1</sup>, R<sup>2</sup> and R<sup>7</sup> are hydrogen.

15 With regard to R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup>, in preferred features of this invention these are independently selected from the following groups: hydrogen, unsubstituted lower alkyl, lower alkyl substituted with a group selected from the group consisting of unsubstituted cycloalkyl, halo, hydroxy,  
20 unsubstituted lower alkoxy, C-carboxy, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted heteroalicyclic, amino, quaternary ammonium or -NR<sup>18</sup>R<sup>19</sup>, unsubstituted cycloalkyl, hydroxy, unsubstituted lower alkyl alkoxy, lower alkyl alkoxy substituted with a group selected from the  
25 group consisting of one or more halo groups, unsubstituted aryl or unsubstituted heteroaryl, trihalomethyl, halo, unsubstituted aryl, aryl substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one  
30 or more halo groups, trihalomethyl, halo, hydroxy, unsubstituted lower alkyl alkoxy, unsubstituted aryloxy, aryloxy substituted with one or more groups independently selected

from the group consisting of halo, unsubstituted lower alkyl, lower alkyl substituted with one or more halo groups, unsubstituted aryl, hydroxy, unsubstituted lower alkoxy, amino or  $-NR^{18}R^{19}$ , amino, S-sulfonamido,  $-NR^{18}R^{19}$ , unsubstituted aryloxy, unsubstituted heteroaryl, heteroaryl substituted with one or more groups independently selected from the group consisting of, hydrogen, unsubstituted lower alkyl, alkyl substituted with one or more halo groups, trihalomethyl, halo, hydroxy, unsubstituted lower alkyl alkoxy, unsubstituted aryloxy, amino, S-sulfonamido or  $-NR^{18}R^{19}$ , unsubstituted heteroalicyclic, heteroalicyclic substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, lower alkyl substituted with one or more halo groups, unsubstituted lower alkoxy, hydroxy, amino, S-sulfonamido or  $-NR^{18}R^{19}$ , unsubstituted lower alkyl C-carboxy, carboxylic acid, unsubstituted lower alkyl carbonyl, aldehyde, unsubstituted aryl carbonyl, acetyl, S-sulfonamido, N-sulfonamido, amino and  $-NR^{18}R^{19}$ .

Additional preferred features of this invention are those in which:

$R^8$ ,  $R^{8'}$  and  $R^{8''}$  are independently selected from the group consisting of hydrogen, unsubstituted lower alkyl, halo, cyano, nitro, C-carboxy, unsubstituted cycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted heteroalicyclic, trihalomethyl, unsubstituted lower alkenyl, unsubstituted lower alkynyl, hydroxy, unsubstituted lower alkyl alkoxy, unsubstituted aryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, carbonyl, C-carboxy, O-carboxy, cyano, nitro, halo, C-amido, N-amido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl, guanidyl, ureidyl,  $-NR^{18}R^{19}$ .

Q has general structure 2, B<sup>1</sup> is nitrogen, B<sup>2</sup> is sulfur or oxygen, n is 0 or 1 and R<sup>9</sup>, R<sup>9'</sup>, R<sup>10</sup>, R<sup>10'</sup>, R<sup>11</sup>, R<sup>11'</sup>, R<sup>12</sup> and R<sup>12'</sup> are hydrogen;

Q has the general structure 2, B<sup>1</sup> and B<sup>2</sup> are nitrogen, n is 0 or 1 and R<sup>7</sup>, R<sup>9</sup>, R<sup>9'</sup>, R<sup>10</sup>, R<sup>10'</sup>, R<sup>11</sup>, R<sup>11'</sup>, R<sup>12</sup> and R<sup>12'</sup> are hydrogen;

Q has the general structure 3, D<sup>1</sup> and D<sup>2</sup> are nitrogen, R<sup>7</sup> is hydrogen or unsubstituted lower alkyl and one of R<sup>8</sup> or R<sup>8'</sup> is selected from the group consisting of -NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>C(=Y)T, -N=CNR<sup>18</sup>R<sup>19</sup> and -NHR<sup>20</sup>, W is oxygen or sulfur, Y is oxygen or sulfur, T is hydroxy, amino, N-hydroxylamino or N-peptidyl, R<sup>18</sup> and R<sup>19</sup> are independently selected from the group consisting of hydrogen and unsubstituted lower alkyl and R<sup>20</sup> is a lower polyhydroxyalkyl group;

Q has the general structure 3, D<sup>1</sup> is nitrogen, D<sup>2</sup> is carbon, R<sup>7</sup> is hydrogen, R<sup>7</sup> is hydrogen or unsubstituted lower alkyl, R<sup>8</sup> and R<sup>8'</sup> are independently hydrogen or unsubstituted lower alkyl and one of R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> is selected from the group consisting of -NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>C(=Y)T, -N=CNR<sup>18</sup>R<sup>19</sup> and -NHR<sup>20</sup>, W is oxygen or sulfur, Y is oxygen or sulfur, T is hydroxy, amino, N-hydroxylamino or N-peptidyl, R<sup>18</sup> and R<sup>19</sup> are independently selected from the group consisting of hydrogen and unsubstituted lower alkyl and R<sup>20</sup> is a lower polyhydroxyalkyl group;

Q has the general structure 3, D<sup>1</sup> is sulfur, R<sup>8</sup> and R<sup>8'</sup>, combined, form an unsubstituted six-member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring and one of R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> is selected from the group consisting of -NR<sup>18</sup>R<sup>19</sup>, -(CH<sub>2</sub>)<sub>m</sub>NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>C(=Y)T, -N=CNR<sup>18</sup>R<sup>19</sup> and -NHR<sup>20</sup>, W is oxygen or sulfur, Y is oxygen or sulfur, T is hydroxy, amino, N-hydroxylamino or N-peptidyl, R<sup>18</sup> and R<sup>19</sup> are inde-

pendently selected from the group consisting of hydrogen and unsubstituted lower alkyl and  $R^{20}$  is a lower polyhydroxyalkyl group;

Q has the general structure 3,  $D^1$  is nitrogen,  $D^2$  is  
5 carbon,  $R^7$  is hydrogen or unsubstituted lower alkyl,  $R^8$ ,  $R^{8'}$  and  $R^{8''}$  are independently selected from the group consisting of hydrogen, unsubstituted lower alkyl or C-carboxy substituted with hydrogen or unsubstituted lower alkyl;

Q has the general structure 3,  $D^1$  is sulfur,  $D^2$  is  
10 carbon or nitrogen,  $R^8$ ,  $R^{8'}$  and  $R^{8''}$  (when  $D^2$  is carbon) are selected from the group consisting of hydrogen, unsubstituted lower alkyl, unsubstituted lower alkenyl, unsubstituted lower alkynyl, unsubstituted cycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, halo, unsubstituted lower  
15 alkyl carbonyl, hydroxy, unsubstituted lower alkyl alkoxy, unsubstituted aryloxy, unsubstituted lower alkyl thioalkoxy, unsubstituted thioaryloxy, nitro, trihalomethanecarbonyl or  $R^8$  and  $R^{8'}$ , combined, form a five-member unsubstituted cycloalkyl, unsubstituted heteroaryl or unsubstituted hetero-  
20 alicyclic group or a six-member unsubstituted cycloalkyl, unsubstituted aryl, unsubstituted heteroaryl or unsubstituted heteroalicyclic group;

Q has the general structure 3 and one of  $A^1$ ,  $A^2$ ,  $A^3$  or  $A^4$  is nitrogen;

25 Q has the general structure 3 and  $A^1$  and  $A^3$  are carbon and  $A^2$  and  $A^4$  are nitrogen;

Q has the general structure 4,  $E^1$  is nitrogen,  $E^2$  is carbon,  $R^7$  is hydrogen,  $R^8$  is hydrogen, unsubstituted lower alkyl, lower alkyl substituted with a group selected from  
30 the group consisting of one or more halogens, C-carboxy substituted with hydrogen or unsubstituted lower alkyl, unsubstituted heteroaryl or unsubstituted heteroalicyclic,



unsubstituted aryl or unsubstituted heteroaryl and  $R^9$ ,  $R^{9'}$ ,  $R^{10}$ ,  $R^{10'}$ ,  $R^{11}$ ,  $R^{11'}$ ,  $R^{12}$  and  $R^{12'}$  are hydrogen;

Q has the general structure 4,  $E^1$  is sulfur,  $E^2$  is carbon,  $R^8$  is selected from the group consisting of hydrogen, unsubstituted lower alkyl, unsubstituted cycloalkyl, unsubstituted alkenyl, C-carboxy substituted with hydrogen or unsubstituted lower alkyl, hydroxy, unsubstituted lower alkoxy, unsubstituted cycloalkyloxy and unsubstituted aryloxy and  $R^9$ ,  $R^{9'}$ ,  $R^{10}$ ,  $R^{10'}$ ,  $R^{11}$ ,  $R^{11'}$ ,  $R^{12}$  and  $R^{12'}$  are hydrogen;

Q has the general structure 4,  $E^1$  is oxygen,  $E^2$  is carbon,  $R^8$  is selected from the group consisting of hydrogen, unsubstituted lower alkyl, unsubstituted cycloalkyl, unsubstituted aryl, cyano or C-carboxy substituted with hydrogen or unsubstituted lower alkyl;

Q has the general structure 5,  $J^1$  is nitrogen or oxygen;  $J^2$ ,  $J^3$  and  $J^4$  are carbon, one of  $R^8$ ,  $R^{8'}$  or  $R^{8''}$  is  $-(alk_1)_rM$ ,  $(alk_1)$  is  $-CH_2-$ ,  $r$  is 1 to 3, inclusive,  $M$  is hydroxy, unsubstituted lower alkyl alkoxy, amino, carboxy substituted with hydrogen or unsubstituted lower alkyl, O-carbamyl, N-carbamyl, C-amido, N-amido, unsubstituted morpholino, unsubstituted piperazinyl, unsubstituted tetrazolo, sulfonyl substituted with hydroxy or unsubstituted lower alkyl, S-sulfonamido, ureido, guanidinyl, guanyl or phosphonyl substituted with hydrogen or unsubstituted lower alkyl,  $R^{18}$  and  $R^{19}$  being independently selected from the group consisting of hydrogen and unsubstituted lower alkyl;

Q has general structure 5,  $J^1$  is nitrogen or oxygen,  $R^7$  (when  $J^1$  is nitrogen, when  $J^1$  is oxygen,  $R^7$  does not exist) is hydrogen,  $A^1$ ,  $A^2$ ,  $A^3$  and  $A^4$  are carbon and one of  $R^8$ ,  $R^{8'}$  or  $R^{8''}$  is  $-(alk_1)_rM$ ,  $(alk_1)$  is  $CH_2$ ,  $r$  is 1 to 3, inclusive,  $M$  is C-carboxy substituted with hydroxy or unsubstituted lower

alkyl, the remaining two of  $R^8$ ,  $R^{8'}$  and  $R^{8''}$  are independently selected from the group consisting of hydrogen, unsubstituted lower alkyl or, combined,  $R^8$  and  $R^{8'}$  or  $R^{8'}$  and  $R^{8''}$  form a six-member unsubstituted cycloalkyl, unsubstituted  
5 aryl, unsubstituted heteroaryl or unsubstituted hetero-  
alicyclic group;

Q had the general structure 5,  $J^1$  and  $J^3$  are nitrogen,  $J^2$  and  $J^4$  are carbon and one of  $R^8$  or  $R^{8''}$  is  $-(alk_1)_rM$ , ( $alk_1$ ) is  $CH_2$ ,  $r$  is 1 to 3, inclusive,  $M$  is carboxy substituted with  
10 hydrogen or unsubstituted lower alkyl;

Q has general structure 6,  $L^1$ ,  $L^2$ ,  $L^3$ ,  $L^4$  and  $L^5$  are carbon, one of  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  is 1-piperazinyl wherein  $R^{21}$ ,  $R^{21'}$ ,  $R^{22}$ ,  $R^{22'}$ ,  $R^{24}$ ,  $R^{24'}$ ,  $R^{25}$  and  $R^{25'}$  are hydrogen,  $R^{23}$  is selected from the group consisting of hydrogen, unsub-  
15 stituted lower alkyl, unsubstituted cycloalkyl, unsubsti-  
tuted aminotriazolo, unsubstituted C-thioamido, carbonyl substituted with hydrogen or unsubstituted lower alkyl, C-carboxy substituted with hydrogen or unsubstituted lower alkyl, C-amido, S-sulfonyl substituted with hydroxyl or  
20 unsubstituted lower alkyl, trihalomethanesulfonyl or S-sulfonamido,  $R^{18}$  and  $R^{19}$  being independently selected from the group consisting of hydrogen and unsubstituted lower alkyl and the remaining of  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are inde-  
pendently selected from the group consisting of hydrogen,  
25 unsubstituted lower alkyl, trihalomethyl, halo, hydroxy, unsubstituted lower alkoxy, unsubstituted aryloxy, unsubsti-  
tuted lower alkyl thioalkoxy or unsubstituted thioaryloxy;

Q has the general structure 6,  $A^1$ ,  $A^2$ ,  $A^3$ ,  $A^4$ ,  $L^1$ ,  $L^2$ ,  $L^3$ ,  $L^4$  and  $L^5$  are carbon,  $R^{15}$  is 1-piperazinyl,  $R^{13}$ ,  $R^{14}$ ,  $R^{16}$ ,  $R^{17}$ ,  
30  $R^{21}$ ,  $R^{21'}$ ,  $R^{22}$ ,  $R^{22'}$ ,  $R^{24}$ ,  $R^{24'}$ ,  $R^{25}$  and  $R^{25'}$  are hydrogen and  $R^{23}$  is selected from the group consisting of hydrogen,

unsubstituted lower alkyl and carbonyl substituted with hydrogen.

Examples of specific compounds of this invention are shown in Tables 1, 2, 3 and 4, below. The compounds in  
5 Tables 1, 2, 3, and 4 are shown by way of example and are not to be construed as limiting the scope of this invention in any manner whatsoever.

Table 1

- 10 3-[3-(2-carboxyethyl-4-methylpyrrol-2-methylidenyl)-2-indolinone
- 3-(2-acetyl-3,4-dimethylpyrrol-5-methylidenyl)-2-indolinone
- 3-[4-(2-methoxycarbonylethyl-3-methylpyrrol-2-methylidenyl)-2-indolinone
- 15 3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-2-indolinone
- 3-[2-ethoxycarbonyl-3-(2-ethoxycarbonylethyl)-4-ethoxycarbonylmethylpyrrol-5-methylidenyl)-2-indolinone
- 3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-2-indolinone
- 20 3-(2-chloro-4-methoxycarbonyl-3-methoxycarbonylmethylpyrrol-5-methylidenyl)-2-indolinone
- 3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-2-indolinone
- 25 3-(4-ethoxycarbonyl-3-methylpyrrol-2-methylidenyl)-2-indolinone
- 3-[4-(2-methoxycarbonylethyl)-3-methylpyrrol-2-methylidenyl]-5,6-dimethoxy-2-indolinone
- 3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone
- 30

3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-  
5-bromo-2-indolinone

3-[4-(2-carboxyethyl)-3,5-dimethylpyrrol-2-methylidenyl]-2-indolinone

5 3-[4-(2-carboxyethyl)-4-methyl pyrrol-2-methylidenyl]-  
2-indolinone.

TABLE 2

3-(thien-2-methylidenyl)-4-aza-2-indolinone					
3-(1-methylpyrrol-2-methylidenyl)-4-aza-2-indolinone					
3-(2-methylthien-5-methylidenyl)-4-aza-2-indolinone					
3-(pyrrol-2-methylidenyl)-4-aza-2-indolinone					
3-(4-methylthien-2-methylidenyl)-4-aza-2-indolinone					
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-4-aza-2-indolinone					
3-(4-(2-methoxycarbonyl-3-methylpyrrol-2-methylidenyl)-4-aza-2-indolinone					
3-(2,4-dimethyl-3-ethylpyrrol-5-methylidenyl)-4-aza-2-indolinone					
3-(2-methylmercaptothien-5-methylidenyl)-4-aza-2-indolinone					
3-(1-methylbenzimidazol-2-methylidenyl)-4-aza-2-indolinone					
3-(2,3-dimethylthien-5-methylidenyl)-4-aza-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-4-aza-2-indolinone					
3-(2-chlorothien-5-methylidenyl)-4-aza-2-indolinone					
3-(2,4-dimethylpyrrol-5-methylidenyl)-4-aza-2-indolinone					
3-(2-nitrothien-5-methylidenyl)-4-aza-2-indolinone					
3-(3,4-dimethylthien-2,3-bithien-2-methylidenyl)-4-aza-2-indolinone					
3-(3-bromothien-2-methylidenyl)-4-aza-2-indolinone					
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-4-aza-2-indolinone					
3-(3-ethoxycarbonyl-1,2,4-trimethylpyrrol-5-methylidenyl)-4-aza-2-indolinone					
3-(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-methylidenyl)-4-aza-2-indolinone					
3-(3,4-dimethylpyrrol-2-methylidenyl)-4-aza-2-indolinone					
3-(2-ethylthien-5-methylidenyl)-4-aza-2-indolinone					
3-(2,4-diethylpyrrol-5-methylidenyl)-4-aza-2-indolinone					
3-(4-methylmercaptothien-2-methylidenyl)-4-aza-2-indolinone					
3-(2-trifluoromethyl-1-(thien-2-yl)methylidenyl)-4-aza-2-indolinone					
3-(2,4-diisopropylpyrrol-5-methylidenyl)-4-aza-2-indolinone					
3-(2,4-dimethylthien-5-methylidenyl)-4-aza-2-indolinone					
3-(2-cyclopropyl-4-methylthien-5-methylidenyl)-4-aza-2-indolinone					
3-(2-ethyl-3-methylthien-5-methylidenyl)-4-aza-2-indolinone					
3-(2-isopropyl-3-methylthien-5-methylidenyl)-4-aza-2-indolinone					
3-(2-cyclohexyl-3-methylthien-5-methylidenyl)-4-aza-2-indolinone					
3-(2-phenylthien-5-methylidenyl)-4-aza-2-indolinone					
3-(3-methyl-2-n-propylthien-5-methylidenyl)-4-aza-2-indolinone					
3-(2-n-butylthien-5-methylidenyl)-4-aza-2-indolinone					

3-(2-benzyl-4-methylthien-5-methylidenyl)-4-aza-2-indolinone				
3-(2-n-propylthien-5-methylidenyl)-4-aza-2-indolinone				
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-4-aza-2-indolinone				
3-(4-methoxycarbonyl-3-methoxycarbonylmethyl-2-methylpyrrol-5-methylidenyl)-4-aza-2-indolinone				
3-[4-(4-chlorobenzoyl)-1-methylpyrrol-2-methylidenyl]-4-aza-2-indolinone				
3-[2-[1-methyl-5-(trifluoromethyl)pyrrol-3-yl]thien-5-methylidenyl]-4-aza-2-indolinone				
3-[2-[1-methyl-3-(trifluoromethyl)pyrrol-5-yl]thien-5-methylidenyl]-4-aza-2-indolinone				
3-(3-phenoxythien-2-methylidenyl)-4-aza-2-indolinone				
3-(4-phenylethynylthien-2-methylidenyl)-4-aza-2-indolinone				
3-(2-phenylethynylthien-2-methylidenyl)-4-aza-2-indolinone				
3-(3-methylbenzothien-2-methylidenyl)-4-aza-2-indolinone				
3-[2-(2-carboxyethyl)-3-methylpyrrol-2-methylidenyl]-4-aza-2-indolinone				
3-(thien-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(1-methylpyrrol-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(2-methylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(pyrrol-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(4-methylthienyl-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-[4-(2-methoxycarbonyl-3-methylpyrrol-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone]				
3-(2,4-dimethyl-3-ethylpyrrol-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(2-methylmercaptothien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(1-methylbenzimidazol-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(2,3-dimethylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(2-chlorothien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(2,4-dimethylpyrrol-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(2-nitrothien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(3,4-dimethylthien-2,3-bithien-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(3-bromothien-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(3-ethoxycarbonyl-1,2,4-trimethylpyrrol-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(3,4-dimethylpyrrol-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				
3-(2-ethylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone				

3-(2,4-diethylpyrrol-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(4-methylmercaptothien-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-[2-trifluoromethyl-1-(thien-2-yl)methylidenyl]-5,7-diaza-6-methyl-2-indolinone			
3-(2,4-diisopropylpyrrol-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2,4-dimethylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2-cyclopropyl-4-methylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2-ethyl-3-methylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2-isopropyl-3-methylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2-cyclohexyl-3-methylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2-phenylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2-methyl-2-n-propylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2-n-butylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2-benzyl-4-methylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2-n-propylthien-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(4-methoxycarbonyl-3-methoxycarbonylmethyl-2-methylpyrrol-5-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-[4-(4-chlorobenzoyl)-1-methylpyrrol-2-methylidenyl]-5,7-diaza-6-methyl-2-indolinone			
3-[2-(1-methyl-5-(trifluoromethyl)pyrrol-3-yl)thien-5-methylidenyl]-5,7-diaza-6-methyl-2-indolinone			
3-[2-[1-methyl-3-(trifluoromethyl)pyrrol-5-yl]thien-5-methylidenyl]-5,7-diaza-6-methyl-2-indolinone			
3-(3-phenoxythien-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(4-phenylethynylthien-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(2-phenylethynylthien-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-(3-methylbenzothien-2-methylidenyl)-5,7-diaza-6-methyl-2-indolinone			
3-[2-(2-carboxyethyl)-3-methylpyrrol-2-methylidenyl]-5,7-diaza-6-methyl-2-indolinone			
3-(thien-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone			
3-(1-methylpyrrol-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone			
3-(2-methylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone			
3-(pyrrol-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone			
3-(4-methylthien-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone			
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone			
3-[4-(2-methoxycarbonyl)-3-methylpyrrol-2-methylidenyl]-5,7-diaza-6-ethylmercapto-2-indolinone			
3-(2,4-dimethyl-3-ethylpyrrol-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone			
3-(2-methylmercaptothien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone			
3-(1-methylbenzimidazol-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone			

3-(2,3-dimethylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-chlorothiophen-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2,4-dimethylpyrrol-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-nitrothien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(3,4-dimethylthieno[2,3-b]thien-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(3-bromothiophen-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(3-ethoxycarbonyl-1,2,4-trimethylpyrrol-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(3,4-dimethylpyrrol-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-ethylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2,4-diethylpyrrol-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(4-methylmercaptothiophen-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-trifluoromethyl-1-(thien-2-yl)methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2,4-disopropylpyrrol-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2,4-dimethylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-cyclopropyl-4-methylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-ethyl-3-methylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-isopropyl-3-methylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-cyclohexyl-3-methylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-phenylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(3-methyl-2-n-propylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-n-butylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-benzyl-4-methylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-n-propylthien-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(4-methoxycarbonyl-3-methoxycarbonylmethyl-2-methylpyrrol-5-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-[4-(4-chlorobenzoyl)-1-methylpyrrol-2-methylidenyl]-5,7-diaza-6-ethylmercapto-2-indolinone		
3-[2-[1-methyl-5-(trifluoromethyl)pyrrol-3-yl]thien-5-methylidenyl]-5,7-diaza-6-ethylmercapto-2-indolinone		
3-[2-[1-methyl-3-(trifluoromethyl)pyrrol-5-yl]thien-5-methylidenyl]-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(3-phenoxythien-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(4-phenylethynylthien-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(2-phenylethynylthien-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		
3-(3-methylbenzothien-2-methylidenyl)-5,7-diaza-6-ethylmercapto-2-indolinone		



3-[2-(2-carboxyethyl)-3-methylpyrrol-2-methylidenyl]-5,7-diaza-6-ethylmercapto-2-indolinone			
3-(thien-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(1-methylpyrrol-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-methylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(pyrrol-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(4-methylthien-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-[4-(2-methoxycarbonyl-3-methylpyrrol-2-methylidenyl)-4-aza-5-methyl-2-indolinone]			
3-(2,4-dimethyl-3-ethylpyrrol-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-methylmercaptothien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(1-methylbenzimidazol-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2,3-dimethylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-chlorothien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2,4-dimethylpyrrol-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-nitrothien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(3,4-dimethylthien-2,3-bithien-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(3-bromothien-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(3-ethoxycarbonyl-1,2,4-trimethylpyrrol-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(3,4-dimethylpyrrol-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-ethylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2,4-diethylpyrrol-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(4-methylmercaptothien-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-[2-trifluoromethyl-1-(thien-2-yl)methylidenyl]-4-aza-5-methyl-2-indolinone			
3-(2,4-diisopropylpyrrol-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2,4-dimethylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-cyclopropyl-4-methylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-ethyl-3-methylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-isopropyl-3-methylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-cyclohexyl-3-methylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-phenylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(3-methyl-2-n-propylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-n-butylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			

3-(2-benzyl-4-methylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-n-propylthien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(4-methoxycarbonyl-3-methoxycarbonylmethyl-2-methylpyrrol-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(4-(4-chlorobenzoyl)-1-methylpyrrol-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-(1-methyl-5-(trifluoromethyl)pyrrol-3-yl)thien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-(1-methyl-3-(trifluoromethyl)pyrrol-5-yl)thien-5-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(3-phenoxythien-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(4-phenylethynylthien-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-phenylethynylthien-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(3-methylbenzothien-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(2-(2-carboxyethyl)-3-methylpyrrol-2-methylidenyl)-4-aza-5-methyl-2-indolinone			
3-(thien-2-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(1-methylpyrrol-2-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2-methylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(pyrrol-2-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(4-methylthien-2-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(4-(2-methoxycarbonyl)ethyl)-3-methylpyrrol-2-methylidenyl]-7-aza-5-nitro-2-indolinone			
3-(2,4-dimethyl-3-ethylpyrrol-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2-methylmercaptiothien-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(1-methylbenzimidazol-2-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2,3-dimethylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2-chlorothien-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2,4-dimethylpyrrol-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2-nitrothien-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(3,4-dimethylthienol[2,3-b]thien-2-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(3-bromothien-2-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2-ethoxycarbonyl-1,2,4-trimethylpyrrol-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(3,4-dimethylpyrrol-2-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2-ethylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2,4-diethylpyrrol-5-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(4-methylmercaptiothien-2-methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2-trifluoromethyl-1-(thien-2-yl)methylidenyl)-7-aza-5-nitro-2-indolinone			
3-(2,4-diisopropylpyrrol-5-methylidenyl)-7-aza-5-nitro-2-indolinone			

3-(2,4-dimethylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-cyclopropyl-4-methylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-ethyl-3-methylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-isopropyl-3-methylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-cyclohexyl-3-methylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-phenylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(3-methyl-2-n-propylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-n-butylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-benzyl-4-methylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-n-propylthien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(4-methoxycarbonyl-3-methoxycarbonylmethyl-2-methylpyrrol-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(4-(4-chlorobenzoyl)-1-methylpyrrol-2-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-[1-methyl-5-(trifluoromethyl)pyrrol-3-yl]thien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-[1-methyl-3-(trifluoromethyl)pyrrol-5-yl]thien-5-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(3-phenoxymethyl-2-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(4-phenylethynylthien-2-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-phenylethynylthien-2-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(3-methylbenzothien-2-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(2-(2-carboxyethyl)-3-methylpyrrol-2-methylidenyl)-7-aza-5-nitro-2-indolinone				
3-(thien-2-methylidenyl)-6-aza-2-indolinone				
3-(1-methylpyrrol-2-methylidenyl)-6-aza-2-indolinone				
3-(2-methylthien-5-methylidenyl)-6-aza-2-indolinone				
3-(pyrrol-2-methylidenyl)-6-aza-2-indolinone				
3-(4-methylthien-2-methylidenyl)-6-aza-2-indolinone				
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-6-aza-2-indolinone				
3-(4-(2-methoxycarbonyl-3-methylpyrrol-2-methylidenyl)-6-aza-2-indolinone				
3-(2,4-dimethyl-3-ethylpyrrol-5-methylidenyl)-6-aza-2-indolinone				
3-(2-methylmercaptothien-5-methylidenyl)-6-aza-2-indolinone				
3-(1-methylbenzimidazol-2-methylidenyl)-6-aza-2-indolinone				
3-(2,3-dimethylthien-5-methylidenyl)-6-aza-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-6-aza-2-indolinone				
3-(2-chlorothien-5-methylidenyl)-6-aza-2-indolinone				
3-(2,4-dimethylpyrrol-5-methylidenyl)-6-aza-2-indolinone				
3-(2-nitrothien-5-methylidenyl)-6-aza-2-indolinone				
3-(3,4-dimethylthien-2,3-bithien-2-methylidenyl)-6-aza-2-indolinone				
3-(3-bromothien-2-methylidenyl)-6-aza-2-indolinone				
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-6-aza-2-indolinone				

3-(3-ethoxycarbonyl-1,2,4-trimethylpyrrol-5-methylidenyl)-6-aza-2-indolinone			
3-(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-methylidenyl)-6-aza-2-indolinone			
3-(3,4-dimethylpyrrol-2-methylidenyl)-6-aza-2-indolinone			
3-(2-ethylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(2,4-diethylpyrrol-5-methylidenyl)-6-aza-2-indolinone			
3-(4-methylmercaptiothien-2-methylidenyl)-6-aza-2-indolinone			
3-(2-trifluoromethyl-1-(thien-2-yl)methylidenyl)-6-aza-2-indolinone			
3-(2,4-diisopropylpyrrol-5-methylidenyl)-6-aza-2-indolinone			
3-(2,4-dimethylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(2-cyclopropyl-4-methylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(2-ethyl-3-methylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(2-isopropyl-3-methylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(2-cyclohexyl-3-methylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(2-phenylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(3-methyl-2-n-propylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(2-n-butylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(2-benzyl-4-methylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(2-n-propylthien-5-methylidenyl)-6-aza-2-indolinone			
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-6-aza-2-indolinone			
3-(4-methoxycarbonyl-3-methoxycarbonylmethyl-2-methylpyrrol-5-methylidenyl)-6-aza-2-indolinone			
3-(4-(4-chlorobenzoyl)-1-methylpyrrol-2-methylidenyl)-6-aza-2-indolinone			
3-(2-[1-methyl-5-(trifluoromethyl)pyrrol-3-yl]thien-5-methylidenyl)-6-aza-2-indolinone			
3-(2-[1-methyl-3-(trifluoromethyl)pyrrol-5-yl]thien-5-methylidenyl)-6-aza-2-indolinone			
3-(3-phenoxythien-2-methylidenyl)-6-aza-2-indolinone			
3-(4-phenylethynylthien-2-methylidenyl)-6-aza-2-indolinone			
3-(2-phenylethynylthien-2-methylidenyl)-6-aza-2-indolinone			
3-(3-methylbenzothien-2-methylidenyl)-6-aza-2-indolinone			
3-(2-(2-carboxyethyl)-3-methylpyrrol-2-methylidenyl)-6-aza-2-indolinone			
3-(thien-2-methylidenyl)-5-aza-2-indolinone			
3-(1-methylpyrrol-2-methylidenyl)-5-aza-2-indolinone			
3-(2-methylthien-5-methylidenyl)-5-aza-2-indolinone			
3-(pyrrol-2-methylidenyl)-5-aza-2-indolinone			
3-(4-methylthien-2-methylidenyl)-5-aza-2-indolinone			
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-5-aza-2-indolinone			
3-(4-(2-methoxycarbonyl)ethyl)-3-methylpyrrol-2-methylidenyl]-5-aza-2-indolinone			
3-(2,4-dimethyl-3-ethylpyrrol-5-methylidenyl)-5-aza-2-indolinone			
3-(2-methylmercaptiothien-5-methylidenyl)-5-aza-2-indolinone			
3-(1-methylbenzimidazol-2-methylidenyl)-5-aza-2-indolinone			

3-(2,3-dimethylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-aza-2-indolinone				
3-(2-chlorothien-5-methylidenyl)-5-aza-2-indolinone				
3-(2,4-dimethylpyrrol-5-methylidenyl)-5-aza-2-indolinone				
3-(2-nitrothien-5-methylidenyl)-5-aza-2-indolinone				
3-(3,4-dimethylthieno[2,3-b]thien-2-methylidenyl)-5-aza-2-indolinone				
3-(3-bromothien-2-methylidenyl)-5-aza-2-indolinone				
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-5-aza-2-indolinone				
3-(3-ethoxycarbonyl-1,2,4-trimethylpyrrol-5-methylidenyl)-5-aza-2-indolinone				
3-(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-methylidenyl)-5-aza-2-indolinone				
3-(3,4-dimethylpyrrol-2-methylidenyl)-5-aza-2-indolinone				
3-(2-ethylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(2,4-diethylpyrrol-5-methylidenyl)-5-aza-2-indolinone				
3-(4-methylmercaptothien-2-methylidenyl)-5-aza-2-indolinone				
3-(2-trifluoromethyl-1-(thien-2-yl)methylidenyl)-5-aza-2-indolinone				
3-(2,4-diisopropylpyrrol-5-methylidenyl)-5-aza-2-indolinone				
3-(2,4-dimethylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(2-cyclopropyl-4-methylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(2-ethyl-3-methylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(2-isopropyl-3-methylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(2-cyclohexyl-3-methylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(2-phenylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(3-methyl-2-n-propylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(2-n-butylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(2-benzyl-4-methylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(2-n-propylthien-5-methylidenyl)-5-aza-2-indolinone				
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-5-aza-2-indolinone				
3-(4-methoxycarbonyl-3-methoxycarbonylmethyl-2-methylpyrrol-5-methylidenyl)-5-aza-2-indolinone				
3-(4-(4-chlorobenzoyl)-1-methylpyrrol-2-methylidenyl)-5-aza-2-indolinone				
3-(2-(1-methyl-5-(trifluoromethyl)pyrrol-3-yl)thien-5-methylidenyl)-5-aza-2-indolinone				
3-(2-(1-methyl-3-(trifluoromethyl)pyrrol-5-yl)thien-5-methylidenyl)-5-aza-2-indolinone				
3-(3-phenoxythien-2-methylidenyl)-5-aza-2-indolinone				
3-(4-phenylethynylthien-2-methylidenyl)-5-aza-2-indolinone				
3-(2-phenylethynylthien-2-methylidenyl)-5-aza-2-indolinone				
3-(3-methylbenzothien-2-methylidenyl)-5-aza-2-indolinone				
3-(2-(2-carboxyethyl)-3-methylpyrrol-2-methylidenyl)-5-aza-2-indolinone				
3-(thien-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone				
3-(1-methylpyrrol-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone				

3-(2-methylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(pyrrol-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(4-methylthien-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(4-(2-methoxycarbonyl)ethyl)-3-methylpyrrol-2-methylidenyl-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2,4-dimethyl-3-ethylpyrrol-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-methylmercaptothien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(1-methylbenzimidazol-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2,3-dimethylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-chlorothien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2,4-dimethylpyrrol-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-nitrothien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(3,4-dimethylthien-2,3-bithien-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(3-bromothien-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(3-ethoxycarbonyl-1,2,4-trimethylpyrrol-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(3,4-dimethylpyrrol-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-ethylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2,4-diethylpyrrol-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(4-methylmercaptothien-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-trifluoromethyl-1-(thien-2-yl)methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2,4-diisopropylpyrrol-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2,4-dimethylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-cyclopropyl-4-methylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-ethyl-3-methylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-isopropyl-3-methylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-cyclohexyl-3-methylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-phenylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(3-methyl-2-n-propylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-n-butylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-benzyl-4-methylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-n-propylthien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(4-methoxycarbonyl-3-methoxycarbonylmethyl-2-methylpyrrol-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(4-(4-chlorobenzoyl)-1-methylpyrrol-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-[1-methyl-5-(trifluoromethyl)pyrrol-3-yl]thien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-[1-methyl-3-(trifluoromethyl)pyrrol-5-yl]thien-5-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			

3-(3-phenoxythien-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(4-phenylethynylthien-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-phenylethynylthien-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(3-methylbenzothien-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(2-(2-carboxyethyl)-3-methylpyrrol-2-methylidenyl)-7-aza-6-methyl-5-(pyrid-4-yl)-2-indolinone			
3-(thien-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(1-methylpyrrol-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-methylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(pyrrol-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(4-methylthien-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(4-(2-methoxycarbonyl-3-methylpyrrol-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2,4-dimethyl-3-ethylpyrrol-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-methylmercaptothien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(1-methylbenzimidazol-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2,3-dimethylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-chlorothien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2,4-dimethylpyrrol-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-nitrothien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(3,4-dimethylthien-2,3-bithien-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(3-bromothien-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(3-ethoxycarbonyl-1,2,4-trimethylpyrrol-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(3,4-dimethylpyrrol-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-ethylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2,4-diethylpyrrol-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(4-methylmercaptothien-2-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-trifluoromethyl-1-(thien-2-yl)methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2,4-disopropylpyrrol-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2,4-dimethylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-cyclopropyl-4-methylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-ethyl-3-methylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-isopropyl-3-methylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-cyclohexyl-3-methylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(2-phenylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone			
3-(3-methyl-2-n-propylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone			

3-(2-n-butylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone				
3-(2-benzyl-4-methylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone				
3-(2-n-propylthien-5-methylidenyl)-5-amino-7-aza-2-indolinone				
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-5-amino-7-aza-2-indolinone				
3-(4-methoxycarbonyl-3-methoxycarbonylmethyl-2-methylpyrrol-5-methylidenyl)-5-amino-7-aza-2-indolinone				
3-(4-(4-chlorobenzoyl)-1-methylpyrrol-2-methylidenyl)-5-amino-7-aza-2-indolinone				
3-[2-[1-methyl-5-(trifluoromethyl)pyrrol-3-yl]thien-5-methylidenyl]-5-amino-7-aza-2-indolinone				
3-[2-[1-methyl-3-(trifluoromethyl)pyrrol-5-yl]thien-5-methylidenyl]-5-amino-7-aza-2-indolinone				
3-(3-phenoxythien-2-methylidenyl)-5-amino-7-aza-2-indolinone				
3-(4-phenylethynylthien-2-methylidenyl)-5-amino-7-aza-2-indolinone				
3-(2-phenylethynylthien-2-methylidenyl)-5-amino-7-aza-2-indolinone				
3-(3-methylbenzothien-2-methylidenyl)-5-amino-7-aza-2-indolinone				
3-[2-(2-carboxyethyl)-3-methylpyrrol-2-methylidenyl]-5-amino-7-aza-2-indolinone				
3-(thien-2-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(1-methylpyrrol-2-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2-methylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(pyrrol-2-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(4-methylthien-2-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-[4-(2-methoxycarbonyl-3-methylpyrrol-2-methylidenyl)-5-acetamido-7-aza-2-indolinone]				
3-(2,4-dimethyl-3-ethylpyrrol-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2-methylmercaptothien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(1-methylbenzimidazol-2-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2,3-dimethylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2-chlorothien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2,4-dimethylpyrrol-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2-nitrothien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(3,4-dimethylthien-2,3-b)thien-2-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(3-bromothien-2-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2-ethoxycarbonyl-1,2,4-trimethylpyrrol-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(3,4-dimethylpyrrol-2-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2-ethylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(2,4-diethylpyrrol-5-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-(4-methylmercaptothien-2-methylidenyl)-5-acetamido-7-aza-2-indolinone				
3-[2-(trifluoromethyl-1-(thien-2-yl)methylidenyl)-5-acetamido-7-aza-2-indolinone]				



3-(2,4-diisopropylpyrrol-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2,4-dimethylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-cyclopropyl-4-methylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-ethyl-3-methylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-isopropyl-3-methylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-cyclohexyl-3-methylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-phenylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(3-methyl-2-n-propylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-n-butylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-benzyl-4-methylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-n-propylthien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(4-methoxycarbonyl-3-methoxycarbonylmethyl-2-methylpyrrol-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(4-(4-chlorobenzoyl)-1-methylpyrrol-2-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-(1-methyl-5-(trifluoromethyl)pyrrol-3-yl)thien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-(1-methyl-3-(trifluoromethyl)pyrrol-5-yl)thien-5-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(3-phenoxythien-2-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(4-phenylethynylthien-2-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-phenylethynylthien-2-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(3-methylbenzothien-2-methylidenyl)-5-acetamido-7-aza-2-indolinone			
3-(2-(2-carboxyethyl)-3-methylpyrrol-2-methylidenyl)-5-acetamido-7-aza-2-indolinone			

TABLE 3

MASTER BARCODE	NAME
10717/H02	3-(2-ethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10717/H03	3-[(thien-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10717/H04	3-[(1-methylpyrrol-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10717/H05	3-(4-fluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10717/H06	3-[(indol-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10717/H07	3-[(2-methylthien-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10717/H08	3-(4-bromobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10717/H09	3-[(pyrrol-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10717/H10	3-(2-hydroxy-6-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10717/H11	3-[(3,4-dibromo-2-methylpyrrol-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10718/H02	3-[(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10718/H03	3-(3-bromo-2-hydroxy-5-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10718/H04	3-[(1-hydroxynaph-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10718/H05	3-[[2-ethoxycarbonyl-3-(2-ethoxycarbonyl)ethyl-4-(ethoxycarbonylmethyl)pyrrol-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10718/H06	3-[(2-methyl-3-ethoxycarbonylfuran-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10718/H07	3-[(2,3-dimethoxycarbonyl-5-methylpyrrol-4-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10718/H08	3-(4-chloro-3-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10718/H09	3-(2,4-dihydroxy-3-methylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10718/H10	3-[(furan-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10718/H11	3-[(2-nitrofuran-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10719/H02	3-(4-ethoxy-3-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10719/H03	3-(3,4-dihydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10719/H04	3-(2,4-dimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10719/H05	3-[(2,4-dimethyl-3-ethylpyrrol-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10719/H06	3-(2,4,6-trimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10719/H07	3-(4-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10719/H08	3-(4-dimethylaminobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10719/H09	3-(2-chloro-4-fluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10719/H10	3-(3-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10719/H11	3-[4-fluoro-2-(trifluoromethyl)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10720/H02	3-(2,4,6-trifluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10720/H03	3-(4-hydroxy-2-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10720/H04	3-(3,4-dimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10720/H05	3-(2-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10720/H06	3-benzylidenyl-5,7-dibromo-4-methyl-2-indolinone
10720/H07	3-[(2-methylmercaptothien-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10720/H08	3-(2,4-dihydroxy-6-methylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10720/H09	3-(3-ethoxy-4-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10720/H10	3-(2-hydroxy-5-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10720/H11	3-[(imidazol-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10721/H02	3-[(1-methylbenzimidazol-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone

10721/H03	3-[(4-chloro-1-methylpyrazol-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10721/H04	3-[(2,3-dimethylthien-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10721/H05	3-[(4,5,6,7-tetrahydroindol-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10721/H06	3-(3-chloromethyl-2-hydroxy-5-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10721/H07	3-[(2-chlorothien-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10721/H08	3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10721/H09	3-(3-t-butyl-4-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10721/H10	3-(3-bromo-5-t-butyl-4-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10721/H11	3-(3,5-di-t-butyl-4-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10722/H02	3-(3-t-butyl-4-hydroxy-5-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10722/H03	3-(2,4,6-trihydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10722/H04	3-[(2-nitrothien-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10722/H05	3-(4-carboxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10722/H06	3-(2,4-difluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10722/H07	3-(3,5-dimethyl-4-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10722/H08	3-(3-t-butyl-5-chloro-4-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10722/H09	3-[(2-nitrothien-4-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10722/H10	3-(4-di-n-butylaminobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10722/H11	3-[4-(trifluoromethyl)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10723/H02	3-(2,3,4-trihydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10723/H03	3-(2-hydroxy-3-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10723/H04	3-(3-bromo-4,5-dihydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10723/H05	3-(3,4-diacetoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10723/H06	3-(4-hydroxy-3-methylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10723/H07	3-(2-bromobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10723/H08	3-(2,4-dihydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10723/H09	3-(2-hydroxy-4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10723/H10	3-(3-bromobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10723/H11	3-(3,5-di-t-butyl-2-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10724/H02	3-[(1-dimethylaminonaph-4-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10724/H03	3-(4-hydroxy-3-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10724/H04	3-(3-hydroxy-4-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10724/H05	3-[(8-hydroxy-2,3,6,7-tetrahydro-1H,5H-benzo[ij]quinolizin-9-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10724/H06	3-(3,5-diisopropyl-4-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10724/H07	3-[(benzo[b]furan-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10724/H08	3-(2-hydroxy-4,6-dimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10724/H09	3-[1-(4-chlorophenyl)pyrrol-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10724/H10	3-[(2-ethylfuran-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10724/H11	3-[(3,4-dimethylthieno[2,3-b]thien-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10725/H02	3-[(3-bromothien-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10725/H03	3-(2-bromo-6-hydroxy-5-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10725/H04	3-[(2-methylfuran-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10725/H05	3-[(3-methylpyrazol-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10725/H06	3-(2-hydroxy-6-methoxy-4-methylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10725/H07	3-[4-(4-formylpiperazin-1-yl)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10725/H08	3-[4-(morpholin-1-yl)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone

10725/H09	3-[(2-chloro-4-methoxycarbonyl-3-(methoxycarbonylmethyl)pyrrol-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10725/H10	3-[(4-bromo-2-(4-chlorophenyl)pyrazol-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10725/H11	3-[(imidazol-4-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10726/H02	3-(2-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10726/H03	3-[(2-ethoxycarbonyl-4-methoxycarbonyl-3-methylpyrrol-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10726/H04	3-(3- <i>t</i> -butyl-4-hydroxy-5-methylbenzylidenyl)-5,7-dibromo-4-methyl-2-
10726/H05	3-[(2-bromofuran-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10726/H06	3-[(1,3-dimethylpyrrol-4-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10726/H07	3-[(5,8-dihydroxy-1,2,3,4-tetrahydronaph-6-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10726/H08	3-(5-fluoro-2-oxindol-3-idenyl)-5,7-dibromo-4-methyl-2-indolinone
10726/H09	3-(2-oxindol-3-idenyl)-5,7-dibromo-4-methyl-2-indolinone
10726/H10	3-[(2-ethylthien-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10726/H11	3-(4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10727/H02	3-(4-diethylaminobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10727/H03	3-[(2,4-diethylpyrrol-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10727/H04	3-(3-bromo-5-chloro-2-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-
10727/H05	3-[2-(4-chlorophenylmercapto)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10727/H06	3-[(5-chlorobenzodioxolan-6-yl)methylidenyl]-5,7-dibromo-4-methyl-2-
10727/H07	3-[(1,4-benzopyranon-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10727/H08	3-(3-cyanobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10727/H09	3-(4-cyanobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10727/H10	3-(2,5-dihydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10727/H11	3-(2,3-dimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10728/H02	3-(2,5-dimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10728/H03	3-(2,6-dimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10728/H04	3-(3,5-dimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10728/H05	3-(4-dimethylamino-2-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10728/H06	3-[(fluoren-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10728/H07	3-[2-fluoro-3-(trifluoromethyl)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10728/H08	3-[2-fluoro-5-(trifluoromethyl)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10728/H09	3-[2-fluoro-6-(trifluoromethyl)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10728/H10	3-(2-carboxymethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10728/H11	3-[(4-methoxybenzodioxolan-6-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10729/H02	3-[(2-methoxynaph-1-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10729/H03	3-[(1-methoxynaph-4-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10729/H04	3-(4-methylmercaptobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10729/H05	3-[(3-methylthien-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10729/H06	3-(3-phenoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10729/H07	3-[(pyrid-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10729/H08	3-[(pyrid-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10729/H09	3-[(pyrid-4-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10729/H10	3-[4-(pyrrolidin-1-yl)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10729/H11	3-[(cyclohexen-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10730/H02	3-(2,3,4-trimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10730/H03	3-(2,4,5-trimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10730/H04	3-(3,4,5-trimethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10730/H05	3-[(1-acetylindol-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone

10730/H06	3-[(6-chloro-1,4-benzofuranon-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10730/H07	3-[2-[(2-chlorophenyl)furan-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-
10730/H08	3-[(2-chloroquinolin-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10730/H09	3-[(6,8-dibromo-1,4-benzofuranon-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10730/H10	3-[(2,5-dimethoxytetrahydrofuran-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10730/H11	3-[(2,3-dimethylfuran-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10731/H02	3-[(9-ethylcarbazol-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10731/H03	3-[(6,7-dimethyl-1,4-benzopyron-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10731/H04	3-[4-(propen-2-yl)cyclohexen-1-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10731/H05	3-[(6-isopropyl-1,4-benzopyron-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10731/H06	3-[(6-methyl-1,4-benzopyron-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10731/H07	3-[(6-nitro-1,4-benzopyron-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-
10731/H08	3-[(pyrimid-2,4-dion-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10731/H09	3-[(5-methoxyindol-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10731/H10	3-(1-methyl-2-oxindol-3-idenyl)-5,7-dibromo-4-methyl-2-indolinone
10731/H11	3-[2-[2-(nitrophenyl)furan-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10732/H02	3-[2-(thien-2-yl)-2-(trifluoromethyl)ethylidenyl]-5,7-dibromo-4-methyl-2-
10732/H03	3-(3,5-diisopropyl-4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10732/H04	3-(3,5-diisopropyl-4-phenoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10732/H05	3-(3-t-butyl-4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10732/H06	3-(4-benzyloxy-3-t-butylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10732/H07	3-(3-bromo-5-t-butyl-4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-
10732/H08	3-(4-benzyloxy-3-bromo-5-t-butylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10732/H09	3-(3-t-butyl-5-chloro-4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-
10732/H10	3-(4-benzyloxy-5-t-butyl-3-chlorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10732/H11	3-(3-t-butyl-5-iodo-4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10733/H02	3-(4-benzyloxy-3-t-butyl-5-iodobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10733/H03	3-(3-t-butyl-4-methoxy-5-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10733/H04	3-(3,5-di-t-butyl-4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10733/H05	3-(4-benzyloxy-3,5-di-t-butylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10733/H06	3-(3,5-dimethyl-4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10733/H07	3-(4-benzyloxy-3,5-dimethylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10733/H08	3-(5-bromo-2-hydroxy-3-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10733/H09	3-(5-bromo-2-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10733/H10	3-(2-hydroxy-5-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10733/H11	3-(4-hydroxy-3-methoxy-2-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-
10734/A02	3-(3-ethoxy-2-hydroxybenzylidenyl)-5,7-dibromo-2-indolinone
10734/A03	3-(3,5-dichloro-2-hydroxybenzylidenyl)-5,7-dibromo-2-indolinone
10734/A04	3-(5-chloro-2-hydroxybenzylidenyl)-5,7-dibromo-2-indolinone
10734/A05	3-(4-diethylamino-2-hydroxybenzylidenyl)-5,7-dibromo-2-indolinone
10734/A06	3-(4-nitrobenzylidenyl)-5,7-dibromo-2-indolinone
10734/A07	3-(3,5-dibromo-2-hydroxybenzylidenyl)-5,7-dibromo-2-indolinone
10734/A08	3-(3-fluoro-2-hydroxybenzylidenyl)-5,7-dibromo-2-indolinone

10734/A09	3-(3-bromo-4-hydroxybenzylidenyl)-5,7-dibromo-2-indolinone
10734/A10	3-(4-t-butylbenzylidenyl)-5,7-dibromo-2-indolinone
10734/A11	3-[(2-bromothien-5-yl)methylidenyl]-5,7-dibromo-2-indolinone
10734/B02	3-(3-ethoxy-2-hydroxybenzylidenyl)-5-iodo-2-indolinone
10734/B03	3-(3,5-dichloro-2-hydroxybenzylidenyl)-5-iodo-2-indolinone
10734/B04	3-(5-chloro-2-hydroxybenzylidenyl)-5-iodo-2-indolinone
10734/B05	3-(4-diethylamino-2-hydroxybenzylidenyl)-5-iodo-2-indolinone
10734/B06	3-(4-nitrobenzylidenyl)-5-iodo-2-indolinone
10734/B07	3-(3,5-dibromo-2-hydroxybenzylidenyl)-5-iodo-2-indolinone
10734/B08	3-(3-fluoro-2-hydroxybenzylidenyl)-5-iodo-2-indolinone
10734/B09	3-(3-bromo-4-hydroxybenzylidenyl)-5-iodo-2-indolinone
10734/B10	3-(4-t-butylbenzylidenyl)-5-iodo-2-indolinone
10734/B11	3-[(2-bromothien-5-yl)methylidenyl]-5-iodo-2-indolinone
10734/C02	3-(3-ethoxy-2-hydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10734/C03	3-(3,5-dichloro-2-hydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10734/C04	3-(5-chloro-2-hydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10734/C05	3-(4-diethylamino-2-hydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10734/C06	3-(4-nitrobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10734/C07	3-(3,5-dibromo-2-hydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10734/C08	3-(3-fluoro-2-hydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10734/C09	3-(3-bromo-4-hydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10734/C10	3-(4-t-butylbenzylidenyl)-5-bromo-4-methyl-2-indolinone
10734/C11	3-[(2-bromothien-5-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10734/D02	3-(3-ethoxy-2-hydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10734/D03	3-(3,5-dichloro-2-hydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10734/D04	3-(5-chloro-2-hydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10734/D05	3-(4-diethylamino-2-hydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10734/D06	3-(4-nitrobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10734/D07	3-(3,5-dibromo-2-hydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10734/D08	3-(3-fluoro-2-hydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10734/D09	3-(3-bromo-4-hydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10734/D10	3-(4-t-butylbenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10734/D11	3-[(2-bromothien-5-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10734/E02	3-(3-ethoxy-2-hydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10734/E03	3-(3,5-dichloro-2-hydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10734/E04	3-(5-chloro-2-hydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10734/E05	3-(4-diethylamino-2-hydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10734/E06	3-(4-nitrobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10734/E07	3-(3,5-dibromo-2-hydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10734/E08	3-(3-fluoro-2-hydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10734/E09	3-(3-bromo-4-hydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10734/E10	3-(4-t-butylbenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10734/E11	3-[(2-bromothien-5-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10734/F02	3-(3-ethoxy-2-hydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10734/F03	3-(3,5-dichloro-2-hydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone

10734/F04	3-(5-chloro-2-hydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10734/F05	3-(4-diethylamino-2-hydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10734/F06	3-(4-nitrobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10734/F07	3-(3,5-dibromo-2-hydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10734/F08	3-(3-fluoro-2-hydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10734/F09	3-(3-bromo-4-hydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10734/F10	3-(4-t-butylbenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10734/F11	3-[(2-bromothien-5-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10734/G02	3-(3-ethoxy-2-hydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10734/G03	3-(3,5-dichloro-2-hydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10734/G04	3-(5-chloro-2-hydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10734/G05	3-(4-diethylamino-2-hydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10734/G06	3-(4-nitrobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10734/G07	3-(3,5-dibromo-2-hydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10734/G08	3-(3-fluoro-2-hydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10734/G09	3-(3-bromo-4-hydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10734/G10	3-(4-t-butylbenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10734/G11	3-[(2-bromothien-5-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10734/H02	3-(3-ethoxy-2-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10734/H03	3-(3,5-dichloro-2-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10734/H04	3-(5-chloro-2-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10734/H05	3-(4-diethylamino-2-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10734/H06	3-(4-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10734/H07	3-(3,5-dibromo-2-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10734/H08	3-(3-fluoro-2-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10734/H09	3-(3-bromo-4-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10734/H10	3-(4-t-butylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10734/H11	3-[(2-bromothien-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10735/A02	3-(2-methylbenzylidenyl)-5,7-dibromo-2-indolinone
10735/A03	3-(3,4-difluorobenzylidenyl)-5,7-dibromo-2-indolinone
10735/A04	3-(3,5-difluorobenzylidenyl)-5,7-dibromo-2-indolinone
10735/A05	3-[(3-(trifluoromethyl)benzylidenyl)-5,7-dibromo-2-indolinone
10735/A06	3-[(3,5-di-(trifluoromethyl)benzylidenyl)-5,7-dibromo-2-indolinone
10735/A07	3-(2-cyanobenzylidenyl)-5,7-dibromo-2-indolinone
10735/A08	3-(2,6-difluorobenzylidenyl)-5,7-dibromo-2-indolinone
10735/A09	3-[(naph-1-yl)methylidenyl]-5,7-dibromo-2-indolinone
10735/A10	3-(2,4-dichlorobenzylidenyl)-5,7-dibromo-2-indolinone
10735/A11	3-[(biphenyl-4-yl)methylidenyl]-5,7-dibromo-2-indolinone
10735/B02	3-(2-methylbenzylidenyl)-5-iodo-2-indolinone
10735/B03	3-(3,4-difluorobenzylidenyl)-5-iodo-2-indolinone
10735/B04	3-(3,5-difluorobenzylidenyl)-5-iodo-2-indolinone
10735/B05	3-[(3-(trifluoromethyl)benzylidenyl)-5-iodo-2-indolinone
10735/B06	3-[(3,5-di-(trifluoromethyl)benzylidenyl)-5-iodo-2-indolinone
10735/B07	3-(2-cyanobenzylidenyl)-5-iodo-2-indolinone
10735/B08	3-(2,6-difluorobenzylidenyl)-5-iodo-2-indolinone
10735/B09	3-[(naph-1-yl)methylidenyl]-5-iodo-2-indolinone
10735/B10	3-(2,4-dichlorobenzylidenyl)-5-iodo-2-indolinone
10735/B11	3-[(biphenyl-4-yl)methylidenyl]-5-iodo-2-indolinone
10735/C02	3-(2-methylbenzylidenyl)-5-bromo-4-methyl-2-indolinone
10735/C03	3-(3,4-difluorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10735/C04	3-(3,5-difluorobenzylidenyl)-5-bromo-4-methyl-2-indolinone

10735/C05	3-[(3-(trifluoromethyl)benzylidenyl)-5-bromo-4-methyl-2-indolinone
10735/C06	3-[(3,5-di-(trifluoromethyl)benzylidenyl)-5-bromo-4-methyl-2-indolinone
10735/C07	3-(2-cyanobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10735/C08	3-(2,6-difluorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10735/C09	3-[(naph-1-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10735/C10	3-(2,4-dichlorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10735/C11	3-[(biphenyl-4-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10735/D02	3-(2-methylbenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10735/D03	3-(3,4-difluorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10735/D04	3-(3,5-difluorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10735/D05	3-[(3-(trifluoromethyl)benzylidenyl)-5-methylaminosulfonyl-2-indolinone
10735/D06	3-[(3,5-di-(trifluoromethyl)benzylidenyl)-5-methylaminosulfonyl-2-indolinone
10735/D07	3-(2-cyanobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10735/D08	3-(2,6-difluorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10735/D09	3-[(naph-1-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10735/D10	3-(2,4-dichlorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10735/D11	3-[(biphenyl-4-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10735/E02	3-(2-methylbenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-
10735/E03	3-(3,4-difluorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10735/E04	3-(3,5-difluorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10735/E05	3-[(3-(trifluoromethyl)benzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10735/E06	3-[(3,5-di-(trifluoromethyl)benzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10735/E07	3-(2-cyanobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10735/E08	3-(2,6-difluorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10735/E09	3-[(naph-1-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10735/E10	3-(2,4-dichlorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10735/E11	3-[(biphenyl-4-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10735/F02	3-(2-methylbenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10735/F03	3-(3,4-difluorobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10735/F04	3-(3,5-difluorobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10735/F05	3-[(3-(trifluoromethyl)benzylidenyl)-5-(morpholin-1-yl)sulfonyl]-2-indolinone
10735/F06	3-[(3,5-di-(trifluoromethyl)benzylidenyl)-5-(morpholin-1-yl)sulfonyl]-2-indolinone
10735/F07	3-(2-cyanobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10735/F08	3-(2,6-difluorobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10735/F09	3-[(naph-1-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10735/F10	3-(2,4-dichlorobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10735/F11	3-[(biphenyl-4-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10735/G02	3-(2-methylbenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10735/G03	3-(3,4-difluorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10735/G04	3-(3,5-difluorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10735/G05	3-[(3-(trifluoromethyl)benzylidenyl)-5-(2-chloroethyl)-2-indolinone
10735/G06	3-[(3,5-di-(trifluoromethyl)benzylidenyl)-5-(2-chloroethyl)-2-indolinone
10735/G07	3-(2-cyanobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10735/G08	3-(2,6-difluorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10735/G09	3-[(naph-1-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone



10735/G10	3-(2,4-dichlorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10735/G11	3-[(biphenyl-4-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10735/H02	3-(2-methylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10735/H03	3-(3,4-difluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10735/H04	3-(3,5-difluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10735/H05	3-[(3-(trifluoromethyl)benzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10735/H06	3-[(3,5-di-(trifluoromethyl)benzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10735/H07	3-(2-cyanobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10735/H08	3-(2,6-difluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10735/H09	3-[(naph-1-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10735/H10	3-(2,4-dichlorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10735/H11	3-[(biphenyl-4-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10736/A02	3-(4-chlorobenzylidenyl)-5,7-dibromo-2-indolinone
10736/A03	3-[2-(trifluoromethyl)benzylidenyl]-5,7-dibromo-2-indolinone
10736/A04	3-(3-methylbenzylidenyl)-5,7-dibromo-2-indolinone
10736/A05	3-(4-methylbenzylidenyl)-5,7-dibromo-2-indolinone
10736/A06	3-(3-chlorobenzylidenyl)-5,7-dibromo-2-indolinone
10736/A07	3-(3-fluorobenzylidenyl)-5,7-dibromo-2-indolinone
10736/A08	3-(2-fluorobenzylidenyl)-5,7-dibromo-2-indolinone
10736/A09	3-(4-ethylbenzylidenyl)-5,7-dibromo-2-indolinone
10736/A10	3-(3-methoxybenzylidenyl)-5,7-dibromo-2-indolinone
10736/A11	3-(2-chlorobenzylidenyl)-5,7-dibromo-2-indolinone
10736/B02	3-(4-chlorobenzylidenyl)-5-iodo-2-indolinone
10736/B03	3-[2-(trifluoromethyl)benzylidenyl]-5-iodo-2-indolinone
10736/B04	3-(3-methylbenzylidenyl)-5-iodo-2-indolinone
10736/B05	3-(4-methylbenzylidenyl)-5-iodo-2-indolinone
10736/B06	3-(3-chlorobenzylidenyl)-5-iodo-2-indolinone
10736/B07	3-(3-fluorobenzylidenyl)-5-iodo-2-indolinone
10736/B08	3-(2-fluorobenzylidenyl)-5-iodo-2-indolinone
10736/B09	3-(4-ethylbenzylidenyl)-5-iodo-2-indolinone
10736/B10	3-(3-methoxybenzylidenyl)-5-iodo-2-indolinone
10736/B11	3-(2-chlorobenzylidenyl)-5-iodo-2-indolinone
10736/C02	3-(4-chlorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10736/C03	3-[2-(trifluoromethyl)benzylidenyl]-5-bromo-4-methyl-2-indolinone
10736/C04	3-(3-methylbenzylidenyl)-5-bromo-4-methyl-2-indolinone
10736/C05	3-(4-methylbenzylidenyl)-5-bromo-4-methyl-2-indolinone
10736/C06	3-(3-chlorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10736/C07	3-(3-fluorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10736/C08	3-(2-fluorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10736/C09	3-(4-ethylbenzylidenyl)-5-bromo-4-methyl-2-indolinone
10736/C10	3-(3-methoxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10736/C11	3-(2-chlorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10736/D02	3-(4-chlorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10736/D03	3-[2-(trifluoromethyl)benzylidenyl]-5-methylaminosulfonyl-2-indolinone
10736/D04	3-(3-methylbenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10736/D05	3-(4-methylbenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10736/D06	3-(3-chlorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10736/D07	3-(3-fluorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10736/D08	3-(2-fluorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10736/D09	3-(4-ethylbenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10736/D10	3-(3-methoxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10736/D11	3-(2-chlorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone

10736/E02	3-(4-chlorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-
10736/E03	3-[2-(trifluoromethyl)benzylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10736/E04	3-(3-methylbenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-
10736/E05	3-(4-methylbenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-
10736/E06	3-(3-chlorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-
10736/E07	3-(3-fluorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10736/E08	3-(2-fluorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10736/E09	3-(4-ethylbenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10736/E10	3-(3-methoxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10736/E11	3-(2-chlorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-
10736/F02	3-(4-chlorobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10736/F03	3-[2-(trifluoromethyl)benzylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10736/F04	3-(3-methylbenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10736/F05	3-(4-methylbenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10736/F06	3-(3-chlorobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10736/F07	3-(3-fluorobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10736/F08	3-(2-fluorobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10736/F09	3-(4-ethylbenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10736/F10	3-(3-methoxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10736/F11	3-(2-chlorobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10736/G02	3-(4-chlorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10736/G03	3-[2-(trifluoromethyl)benzylidenyl]-5-(2-chloroethyl)-2-indolinone
10736/G04	3-(3-methylbenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10736/G05	3-(4-methylbenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10736/G06	3-(3-chlorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10736/G07	3-(3-fluorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10736/G08	3-(2-fluorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10736/G09	3-(4-ethylbenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10736/G10	3-(3-methoxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10736/G11	3-(2-chlorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10736/H02	3-(4-chlorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10736/H03	3-[2-(trifluoromethyl)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10736/H04	3-(3-methylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10736/H05	3-(4-methylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10736/H06	3-(3-chlorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10736/H07	3-(3-fluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10736/H08	3-(2-fluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10736/H09	3-(4-ethylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10736/H10	3-(3-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10736/H11	3-(2-chlorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10737/A02	3-(4-ethoxybenzylidenyl)-5,7-dibromo-2-indolinone
10737/A03	3-(2,4-dimethylbenzylidenyl)-5,7-dibromo-2-indolinone
10737/A04	3-(2,5-difluorobenzylidenyl)-5,7-dibromo-2-indolinone
10737/A05	3-(2,3-difluorobenzylidenyl)-5,7-dibromo-2-indolinone
10737/A06	3-(3-fluoro-4-methoxybenzylidenyl)-5,7-dibromo-2-indolinone
10737/A07	3-(2,5-dimethylbenzylidenyl)-5,7-dibromo-2-indolinone
10737/A08	3-[(naph-2-yl)methylidenyl]-5,7-dibromo-2-indolinone
10737/A09	3-(4-phenoxybenzylidenyl)-5,7-dibromo-2-indolinone
10737/A10	3-[3-(4-t-butylphenoxy)benzylidenyl]-5,7-dibromo-2-indolinone
10737/A11	3-[3-(3-(trifluoromethyl)phenoxy)benzylidenyl]-5,7-dibromo-2-indolinone

10737/B02	3-(4-ethoxybenzylidenyl)-5-iodo-2-indolinone
10737/B03	3-(2,4-dimethylbenzylidenyl)-5-iodo-2-indolinone
10737/B04	3-(2,5-difluorobenzylidenyl)-5-iodo-2-indolinone
10737/B05	3-(2,3-difluorobenzylidenyl)-5-iodo-2-indolinone
10737/B06	3-(3-fluoro-4-methoxybenzylidenyl)-5-iodo-2-indolinone
10737/B07	3-(2,5-dimethylbenzylidenyl)-5-iodo-2-indolinone
10737/B08	3-[(naph-2-yl)methylidenyl]-5-iodo-2-indolinone
10737/B09	3-(4-phenoxybenzylidenyl)-5-iodo-2-indolinone
10737/B10	3-[3-(4-t-butylphenoxy)benzylidenyl]-5-iodo-2-indolinone
10737/B11	3-[3-(3-(trifluoromethyl)phenoxy)benzylidenyl]-5-iodo-2-indolinone
10737/C02	3-(4-ethoxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10737/C03	3-(2,4-dimethylbenzylidenyl)-5-bromo-4-methyl-2-indolinone
10737/C04	3-(2,5-difluorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10737/C05	3-(2,3-difluorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10737/C06	3-(3-fluoro-4-methoxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10737/C07	3-(2,5-dimethylbenzylidenyl)-5-bromo-4-methyl-2-indolinone
10737/C08	3-[(naph-2-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10737/C09	3-(4-phenoxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10737/C10	3-[3-(4-t-butylphenoxy)benzylidenyl]-5-bromo-4-methyl-2-indolinone
10737/C11	3-[3-(3-(trifluoromethyl)phenoxy)benzylidenyl]-5-bromo-4-methyl-2-indolinone
10737/D02	3-(4-ethoxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10737/D03	3-(2,4-dimethylbenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10737/D04	3-(2,5-difluorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10737/D05	3-(2,3-difluorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10737/D06	3-(3-fluoro-4-methoxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10737/D07	3-(2,5-dimethylbenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10737/D08	3-[(naph-2-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10737/D09	3-(4-phenoxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10737/D10	3-[3-(4-t-butylphenoxy)benzylidenyl]-5-methylaminosulfonyl-2-indolinone
10737/D11	3-[3-(3-(trifluoromethyl)phenoxy)benzylidenyl]-5-methylaminosulfonyl-2-indolinone
10737/E02	3-(4-ethoxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10737/E03	3-(2,4-dimethylbenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10737/E04	3-(2,5-difluorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10737/E05	3-(2,3-difluorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10737/E06	3-(3-fluoro-4-methoxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10737/E07	3-(2,5-dimethylbenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10737/E08	3-[(naph-2-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10737/E09	3-(4-phenoxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10737/E10	3-[3-(4-t-butylphenoxy)benzylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10737/E11	3-[3-(3-(trifluoromethyl)phenoxy)benzylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10737/F02	3-(4-ethoxybenzylidenyl)-5-(mopropholin-1-yl)sulfonyl-2-indolinone
10737/F03	3-(2,4-dimethylbenzylidenyl)-5-(mopropholin-1-yl)sulfonyl-2-indolinone
10737/F04	3-(2,5-difluorobenzylidenyl)-5-(mopropholin-1-yl)sulfonyl-2-indolinone

10737/F05	3-(2,3-difluorobenzylidenyl)-5-(moprholin-1-yl)sulfonyl-2-indolinone
10737/F06	3-(3-fluoro-4-methoxybenzylidenyl)-5-(moprholin-1-yl)sulfonyl-2-indolinone
10737/F07	3-(2,5-dimethylbenzylidenyl)-5-(moprholin-1-yl)sulfonyl-2-indolinone
10737/F08	3-[(naph-2-yl)methylidenyl]-5-(moprholin-1-yl)sulfonyl-2-indolinone
10737/F09	3-(4-phenoxybenzylidenyl)-5-(moprholin-1-yl)sulfonyl-2-indolinone
10737/F10	3-[3-(4-t-butylphenoxy)benzylidenyl]-5-(moprholin-1-yl)sulfonyl-2-indolinone
10737/F11	3-[3-(3-(trifluoromethyl)phenoxy)benzylidenyl]-5-(moprholin-1-yl)sulfonyl-2-indolinone
10737/G02	3-(4-ethoxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10737/G03	3-(2,4-dimethylbenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10737/G04	3-(2,5-difluorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10737/G05	3-(2,3-difluorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10737/G06	3-(3-fluoro-4-methoxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10737/G07	3-(2,5-dimethylbenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10737/G08	3-[(naph-2-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10737/G09	3-(4-phenoxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10737/G10	3-[3-(4-t-butylphenoxy)benzylidenyl]-5-(2-chloroethyl)-2-indolinone
10737/G11	3-[3-(3-(trifluoromethyl)phenoxy)benzylidenyl]-5-(2-chloroethyl)-2-indolinone
10737/H02	3-(4-ethoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10737/H03	3-(2,4-dimethylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10737/H04	3-(2,5-difluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10737/H05	3-(2,3-difluorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10737/H06	3-(3-fluoro-4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10737/H07	3-(2,5-dimethylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10737/H08	3-[(naph-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10737/H09	3-(4-phenoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10737/H10	3-[3-(4-t-butylphenoxy)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10737/H11	3-[3-(3-(trifluoromethyl)phenoxy)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10738/A02	3-[3-(4-methylphenoxy)benzylidenyl]-5,7-dibromo-2-indolinone
10738/A03	3-[3-(3,4-dichlorophenoxy)benzylidenyl]-5,7-dibromo-2-indolinone
10738/A04	3-(3-hydroxy-4-methoxybenzylidenyl)-5,7-dibromo-2-indolinone
10738/A05	3-(5-hydroxy-2-nitrobenzylidenyl)-5,7-dibromo-2-indolinone
10738/A06	3-(2,3-dihydroxybenzylidenyl)-5,7-dibromo-2-indolinone
10738/A07	3-(3,5-dihydroxybenzylidenyl)-5,7-dibromo-2-indolinone
10738/A08	3-(3,4-dichlorobenzylidenyl)-5,7-dibromo-2-indolinone
10738/A09	3-(2-methoxybenzylidenyl)-5,7-dibromo-2-indolinone
10738/A10	3-(4-isopropylbenzylidenyl)-5,7-dibromo-2-indolinone
10738/A11	3-(4-n-propoxybenzylidenyl)-5,7-dibromo-2-indolinone
10738/B02	3-[3-(4-methylphenoxy)benzylidenyl]-5-iodo-2-indolinone
10738/B03	3-[3-(3,4-dichlorophenoxy)benzylidenyl]-5-iodo-2-indolinone
10738/B04	3-(3-hydroxy-4-methoxybenzylidenyl)-5-iodo-2-indolinone
10738/B05	3-(5-hydroxy-2-nitrobenzylidenyl)-5-iodo-2-indolinone
10738/B06	3-(2,3-dihydroxybenzylidenyl)-5-iodo-2-indolinone
10738/B07	3-(3,5-dihydroxybenzylidenyl)-5-iodo-2-indolinone
10738/B08	3-(3,4-dichlorobenzylidenyl)-5-iodo-2-indolinone
10738/B09	3-(2-methoxybenzylidenyl)-5-iodo-2-indolinone
10738/B10	3-(4-isopropylbenzylidenyl)-5-iodo-2-indolinone
10738/B11	3-(4-n-propoxybenzylidenyl)-5-iodo-2-indolinone
10738/C02	3-[3-(4-methylphenoxy)benzylidenyl]-5-bromo-4-methyl-2-indolinone
10738/C03	3-[3-(3,4-dichlorophenoxy)benzylidenyl]-5-bromo-4-methyl-2-indolinone
10738/C04	3-(3-hydroxy-4-methoxybenzylidenyl)-5-bromo-4-methyl-2-indolinone

10738/C05	3-(5-hydroxy-2-nitrobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10738/C06	3-(2,3-dihydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10738/C07	3-(3,5-dihydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10738/C08	3-(3,4-dichlorobenzylidenyl)-5-bromo-4-methyl-2-indolinone
10738/C09	3-(2-methoxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10738/C10	3-(4-isopropylbenzylidenyl)-5-bromo-4-methyl-2-indolinone
10738/C11	3-(4-n-propoxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10738/D02	3-[3-(4-methylphenoxy)benzylidenyl]-5-methylaminosulfonyl-2-indolinone
10738/D03	3-[3-(3,4-dichlorophenoxy)benzylidenyl]-5-methylaminosulfonyl-2-indolinone
10738/D04	3-(3-hydroxy-4-methoxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10738/D05	3-(5-hydroxy-2-nitrobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10738/D06	3-(2,3-dihydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10738/D07	3-(3,5-dihydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10738/D08	3-(3,4-dichlorobenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10738/D09	3-(2-methoxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10738/D10	3-(4-isopropylbenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10738/D11	3-(4-n-propoxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10738/E02	3-[3-(4-methylphenoxy)benzylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10738/E03	3-[3-(3,4-dichlorophenoxy)benzylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10738/E04	3-(3-hydroxy-4-methoxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10738/E05	3-(5-hydroxy-2-nitrobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10738/E06	3-(2,3-dihydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10738/E07	3-(3,5-dihydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10738/E08	3-(3,4-dichlorobenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10738/E09	3-(2-methoxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10738/E10	3-(4-isopropylbenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10738/E11	3-(4-n-propoxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10738/F02	3-[3-(4-methylphenoxy)benzylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10738/F03	3-[3-(3,4-dichlorophenoxy)benzylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10738/F04	3-(3-hydroxy-4-methoxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10738/F05	3-(5-hydroxy-2-nitrobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10738/F06	3-(2,3-dihydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10738/F07	3-(3,5-dihydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10738/F08	3-(3,4-dichlorobenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10738/F09	3-(2-methoxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10738/F10	3-(4-isopropylbenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10738/F11	3-(4-n-propoxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10738/G02	3-[3-(4-methylphenoxy)benzylidenyl]-5-(2-chloroethyl)-2-indolinone
10738/G03	3-[3-(3,4-dichlorophenoxy)benzylidenyl]-5-(2-chloroethyl)-2-indolinone
10738/G04	3-(3-hydroxy-4-methoxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10738/G05	3-(5-hydroxy-2-nitrobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10738/G06	3-(2,3-dihydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10738/G07	3-(3,5-dihydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone

10738/G08	3-(3,4-dichlorobenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10738/G09	3-(2-methoxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10738/G10	3-(4-isopropylbenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10738/G11	3-(4-n-propoxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10738/H02	3-[3-(4-methylphenoxy)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10738/H03	3-[3-(3,4-dichlorophenoxy)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10738/H04	3-(3-hydroxy-4-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10738/H05	3-(5-hydroxy-2-nitrobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10738/H06	3-(2,3-dihydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10738/H07	3-(3,5-dihydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10738/H08	3-(3,4-dichlorobenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10738/H09	3-(2-methoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10738/H10	3-(4-isopropylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10738/H11	3-(4-n-propoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10739/A02	3-(4-methoxy-3-methylbenzylidenyl)-5,7-dibromo-2-indolinone
10739/A03	3-(3-benzyloxybenzylidenyl)-5,7-dibromo-2-indolinone
10739/A04	3-(4-benzyloxybenzylidenyl)-5,7-dibromo-2-indolinone
10739/A05	3-[(1,4-benzodioxan-3-yl)methylidenyl]-5,7-dibromo-2-indolinone
10739/A06	3-(2-chloro-4-hydroxybenzylidenyl)-5,7-dibromo-2-indolinone
10739/A07	3-(3,4,5-trihydroxybenzylidenyl)-5,7-dibromo-2-indolinone
10739/A08	3-[3-(4-methoxyphenoxy)benzylidenyl]-5,7-dibromo-2-indolinone
10739/A09	3-[4-(3-dimethylamino-n-propoxy)benzylidenyl]-5,7-dibromo-2-indolinone
10739/A10	3-[(furan-3-yl)methylidenyl]-5,7-dibromo-2-indolinone
10739/A11	3-[(2-hydroxymethylfuran-5-yl)methylidenyl]-5,7-dibromo-2-indolinone
10739/B02	3-(4-methoxy-3-methylbenzylidenyl)-5-iodo-2-indolinone
10739/B03	3-(3-benzyloxybenzylidenyl)-5-iodo-2-indolinone
10739/B04	3-(4-benzyloxybenzylidenyl)-5-iodo-2-indolinone
10739/B05	3-[(1,4-benzodioxan-3-yl)methylidenyl]-5-iodo-2-indolinone
10739/B06	3-(2-chloro-4-hydroxybenzylidenyl)-5-iodo-2-indolinone
10739/B07	3-(3,4,5-trihydroxybenzylidenyl)-5-iodo-2-indolinone
10739/B08	3-[3-(4-methoxyphenoxy)benzylidenyl]-5-iodo-2-indolinone
10739/B09	3-[4-(3-dimethylamino-n-propoxy)benzylidenyl]-5-iodo-2-indolinone
10739/B10	3-[(furan-3-yl)methylidenyl]-5-iodo-2-indolinone
10739/B11	3-[(2-hydroxymethylfuran-5-yl)methylidenyl]-5-iodo-2-indolinone
10739/C02	3-(4-methoxy-3-methylbenzylidenyl)-5-bromo-4-methyl-2-indolinone
10739/C03	3-(3-benzyloxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10739/C04	3-(4-benzyloxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10739/C05	3-[(1,4-benzodioxan-3-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10739/C06	3-(2-chloro-4-hydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10739/C07	3-(3,4,5-trihydroxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10739/C08	3-[3-(4-methoxyphenoxy)benzylidenyl]-5-bromo-4-methyl-2-indolinone
10739/C09	3-[4-(3-dimethylamino-n-propoxy)benzylidenyl]-5-bromo-4-methyl-2-indolinone
10739/C10	3-[(furan-3-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10739/C11	3-[(2-hydroxymethylfuran-5-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10739/D02	3-(4-methoxy-3-methylbenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10739/D03	3-(3-benzyloxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10739/D04	3-(4-benzyloxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10739/D05	3-[(1,4-benzodioxan-3-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10739/D06	3-(2-chloro-4-hydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10739/D07	3-(3,4,5-trihydroxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10739/D08	3-[3-(4-methoxyphenoxy)benzylidenyl]-5-methylaminosulfonyl-2-indolinone

10739/D09	3-[4-(3-dimethylamino-n-propoxy)benzylidenyl]-5-methylaminosulfonyl-2-indolinone
10739/D10	3-[(furan-3-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10739/D11	3-[(2-hydroxymethylfuran-5-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10739/E02	3-(4-methoxy-3-methylbenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10739/E03	3-(3-benzyloxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10739/E04	3-(4-benzyloxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10739/E05	3-[(1,4-benzodioxan-3-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10739/E06	3-(2-chloro-4-hydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10739/E07	3-(3,4,5-trihydroxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10739/E08	3-[3-(4-methoxyphenoxy)benzylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10739/E09	3-[4-(3-dimethylamino-n-propoxy)benzylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10739/E10	3-[(furan-3-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10739/E11	3-[(2-hydroxymethylfuran-5-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10739/F02	3-(4-methoxy-3-methylbenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10739/F03	3-(3-benzyloxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10739/F04	3-(4-benzyloxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10739/F05	3-[(1,4-benzodioxan-3-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10739/F06	3-(2-chloro-4-hydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10739/F07	3-(3,4,5-trihydroxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10739/F08	3-[3-(4-methoxyphenoxy)benzylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10739/F09	3-[4-(3-dimethylamino-n-propoxy)benzylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10739/F10	3-[(furan-3-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10739/F11	3-[(2-hydroxymethylfuran-5-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10739/G02	3-(4-methoxy-3-methylbenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10739/G03	3-(3-benzyloxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10739/G04	3-(4-benzyloxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10739/G05	3-[(1,4-benzodioxan-3-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10739/G06	3-(2-chloro-4-hydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10739/G07	3-(3,4,5-trihydroxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10739/G08	3-[3-(4-methoxyphenoxy)benzylidenyl]-5-(2-chloroethyl)-2-indolinone
10739/G09	3-[4-(3-dimethylamino-n-propoxy)benzylidenyl]-5-(2-chloroethyl)-2-indolinone
10739/G10	3-[(furan-3-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10739/G11	3-[(2-hydroxymethylfuran-5-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10739/H02	3-(4-methoxy-3-methylbenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10739/H03	3-(3-benzyloxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10739/H04	3-(4-benzyloxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10739/H05	3-[(1,4-benzodioxan-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10739/H06	3-(2-chloro-4-hydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10739/H07	3-(3,4,5-trihydroxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone
10739/H08	3-[3-(4-methoxyphenoxy)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone

10739/H09	3-[4-(3-dimethylamino-n-propoxy)benzylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10739/H10	3-[(furan-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10739/H11	3-[(2-hydroxymethylfuran-5-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10740/A02	3-[(quinolin-3-yl)methylidenyl]-5,7-dibromo-2-indolinone
10740/A03	3-[(quinolin-4-yl)methylidenyl]-5,7-dibromo-2-indolinone
10740/A04	3-[(2-methoxypyrrolidin-1-yl)methylidenyl]-5,7-dibromo-2-indolinone
10740/A05	3-[(thien-3-yl)methylidenyl]-5,7-dibromo-2-indolinone
10740/A06	3-[(quinolin-2-yl)methylidenyl]-5,7-dibromo-2-indolinone
10740/A07	3-[(1-methylindol-3-yl)methylidenyl]-5,7-dibromo-2-indolinone
10740/A08	3-[(2-methylindol-3-yl)methylidenyl]-5,7-dibromo-2-indolinone
10740/A09	3-[(1-methylpyrid-6-yl)methylidenyl]-5,7-dibromo-2-indolinone
10740/A10	3-[(4-bromothien-2-yl)methylidenyl]-5,7-dibromo-2-indolinone
10740/A11	3-(4-n-butoxybenzylidenyl)-5,7-dibromo-2-indolinone
10740/B02	3-[(quinolin-3-yl)methylidenyl]-5-iodo-2-indolinone
10740/B03	3-[(quinolin-4-yl)methylidenyl]-5-iodo-2-indolinone
10740/B04	3-[(2-methoxypyrrolidin-1-yl)methylidenyl]-5-iodo-2-indolinone
10740/B05	3-[(thien-3-yl)methylidenyl]-5-iodo-2-indolinone
10740/B06	3-[(quinolin-2-yl)methylidenyl]-5-iodo-2-indolinone
10740/B07	3-[(1-methylindol-3-yl)methylidenyl]-5-iodo-2-indolinone
10740/B08	3-[(2-methylindol-3-yl)methylidenyl]-5-iodo-2-indolinone
10740/B09	3-[(1-methylpyrid-6-yl)methylidenyl]-5-iodo-2-indolinone
10740/B10	3-[(4-bromothien-2-yl)methylidenyl]-5-iodo-2-indolinone
10740/B11	3-(4-n-butoxybenzylidenyl)-5-iodo-2-indolinone
10740/C02	3-[(quinolin-3-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10740/C03	3-[(quinolin-4-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10740/C04	3-[(2-methoxypyrrolidin-1-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10740/C05	3-[(thien-3-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10740/C06	3-[(quinolin-2-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10740/C07	3-[(1-methylindol-3-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10740/C08	3-[(2-methylindol-3-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10740/C09	3-[(1-methylpyrid-6-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10740/C10	3-[(4-bromothien-2-yl)methylidenyl]-5-bromo-4-methyl-2-indolinone
10740/C11	3-(4-n-butoxybenzylidenyl)-5-bromo-4-methyl-2-indolinone
10740/D02	3-[(quinolin-3-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10740/D03	3-[(quinolin-4-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10740/D04	3-[(2-methoxypyrrolidin-1-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10740/D05	3-[(thien-3-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10740/D06	3-[(quinolin-2-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10740/D07	3-[(1-methylindol-3-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10740/D08	3-[(2-methylindol-3-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10740/D09	3-[(1-methylpyrid-6-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10740/D10	3-[(4-bromothien-2-yl)methylidenyl]-5-methylaminosulfonyl-2-indolinone
10740/D11	3-(4-n-butoxybenzylidenyl)-5-methylaminosulfonyl-2-indolinone
10740/E02	3-[(quinolin-3-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10740/E03	3-[(quinolin-4-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10740/E04	3-[(2-methoxypyrrolidin-1-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10740/E05	3-[(thien-3-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone



10740/E06	3-[(quinolin-2-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10740/E07	3-[(1-methylindol-3-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10740/E08	3-[(2-methylindol-3-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10740/E09	3-[(1-methylpyrid-6-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10740/E10	3-[(4-bromothien-2-yl)methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10740/E11	3-(4-n-butoxybenzylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone
10740/F02	3-[(quinolin-3-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10740/F03	3-[(quinolin-4-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10740/F04	3-[(2-methoxypyrrolidin-1-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10740/F05	3-[(thien-3-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10740/F06	3-[(quinolin-2-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10740/F07	3-[(1-methylindol-3-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10740/F08	3-[(2-methylindol-3-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10740/F09	3-[(1-methylpyrid-6-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10740/F10	3-[(4-bromothien-2-yl)methylidenyl]-5-(morpholin-1-yl)sulfonyl-2-indolinone
10740/F11	3-(4-n-butoxybenzylidenyl)-5-(morpholin-1-yl)sulfonyl-2-indolinone
10740/G02	3-[(quinolin-3-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10740/G03	3-[(quinolin-4-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10740/G04	3-[(2-methoxypyrrolidin-1-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10740/G05	3-[(thien-3-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10740/G06	3-[(quinolin-2-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10740/G07	3-[(1-methylindol-3-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10740/G08	3-[(2-methylindol-3-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10740/G09	3-[(1-methylpyrid-6-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10740/G10	3-[(4-bromothien-2-yl)methylidenyl]-5-(2-chloroethyl)-2-indolinone
10740/G11	3-(4-n-butoxybenzylidenyl)-5-(2-chloroethyl)-2-indolinone
10740/H02	3-[(quinolin-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10740/H03	3-[(quinolin-4-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10740/H04	3-[(2-methoxypyrrolidin-1-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10740/H05	3-[(thien-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10740/H06	3-[(quinolin-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10740/H07	3-[(1-methylindol-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10740/H08	3-[(2-methylindol-3-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10740/H09	3-[(1-methylpyrid-6-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10740/H10	3-[(4-bromothien-2-yl)methylidenyl]-5,7-dibromo-4-methyl-2-indolinone
10740/H11	3-(4-n-butoxybenzylidenyl)-5,7-dibromo-4-methyl-2-indolinone

TABLE 4

3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-amino-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-amino-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			

3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-pyrrolidin-1-ethyl)-2-indolinone			



3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidene)-5-(piperidin-1-ethyl)-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidene)-5-(piperidin-1-ethyl)-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidene)-5-(piperidin-1-ethyl)-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidene)-5-(piperidin-1-ethyl)-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidene)-5-(piperidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidene)-5-(piperidin-1-ethyl)-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidene)-5-(piperidin-1-ethyl)-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidene)-5-(piperidin-1-ethyl)-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidene)-5-(2-piperidin-1-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(3-(isochinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidene)-5-trifluoromethyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidene)-5-trifluoromethyl-2-indolinone			

3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(piperidin-1-acyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-(3-isopropylamino-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			

3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxy-2-indolinone			
3-[3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-methoxy-2-indolinone			
3-[3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-methoxy-2-indolinone			
3-[3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-methoxy-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxy-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-[3-(4-methylphenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-trifluoromethyl-2-indolinone			
3-[3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-trifluoromethyl-2-indolinone			
3-[3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-trifluoromethyl-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-trifluoromethyl-2-indolinone			

[illegible]



3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxy-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxy-2-indolinone					
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxy-2-indolinone					
3-(3-phenylsulfonylmethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxy-2-indolinone					
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxy-2-indolinone					
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxy-2-indolinone					
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxy-2-indolinone					
3-(3-phenylaminomethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxy-2-indolinone					
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxy-2-indolinone					
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-(isouinol-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone					

[illegible]

3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone			
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-ethyl-2-indolinone			

3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-ethyl-2-indolinone					
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-ethyl-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-ethyl-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-ethyl-2-indolinone					
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-ethyl-2-indolinone					
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-ethyl-2-indolinone					
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-ethyl-2-indolinone					
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-ethyl-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone					
3-(4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone					
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone					
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone					
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone					
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone					
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-ethyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-(2-morpholin-4-ethyl)-2-indolinone					

3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-[3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl]-5-n-butyl-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-n-butyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-ethyl-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-ethyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-ethyl-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-ethyl-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-ethyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-ethyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-ethyl-2-indolinone			
3-[3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-ethyl-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-ethyl-2-indolinone			

3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-ethyl-2-indolinone				
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-ethyl-2-indolinone				
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-ethyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-ethyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-ethyl-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-(isouquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-n-butyl-2-indolinone				
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-n-butyl-2-indolinone				

3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-n-butyl-2-indolinone					
3-(3-(isouquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					

3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-[3-(4-methylphenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-[3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5,7-dibromo-4-methyl-2-indolinone					
3-[3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5,7-dibromo-4-methyl-2-indolinone					
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-4-methyl-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-[3-(isouinol-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl]-5-(2-carboxyethyl)-2-indolinone					
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-[3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-(2-carboxyethyl)-2-indolinone					



3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone	
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-4-methyl-2-indolinone	
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone	
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone	
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-carboxy-2-indolinone	

3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-carboxy-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-carboxy-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone					
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone					
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone					
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone					
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone					
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-phenylphenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					

3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-carboxy-2-indolinone					
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone					
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone					

3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone			
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone			
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone			
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-carboxy-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-carboxy-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-carboxy-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone			
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-carboxy-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-chloroethyl)-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			

3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methoxycarbonyl-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone			

[illegible]

3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone				
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone				
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone				
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone				
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone				
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone				
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-(isquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-6-trifluoromethyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-6-trifluoromethyl-2-indolinone				

[illegible]



3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone					
3-[3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl]-5-(morpholin-4-sulfonyl)-2-indolinone					
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone					
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone					
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(morpholin-4-sulfonyl)-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					
3-[3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					
3-[3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					
3-[3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-[4-(trifluoromethyl)phenylaminosulfonyl]-2-indolinone					

[illegible]

3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-[3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-methylaminosulfonyl-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-[3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-methylaminosulfonyl-2-indolinone			
3-[3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-methylaminosulfonyl-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-[3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl]-5-methylaminosulfonyl-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methylaminosulfonyl-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-[3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-[3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-[3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			

[illegible]

3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)-4-methyl-2-indolinone			

	3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)4-methyl-2-indolinone	
	3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)4-methyl-2-indolinone	
	3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-(2-carboxyethyl)4-methyl-2-indolinone	
	3-(3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone	
	3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone	
	3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-6-fluoro-2-indolinone	

3-[3-(isoquinolin-1-ylmethyl)-4,5,6,7-tetrahydroindol-2-ylmethylidene]-6-fluoro-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-ylmethylidene)-6-fluoro-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-ylmethylidene)-6-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-ylmethylidene)-6-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-ylmethylidene)-6-fluoro-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-ylmethylidene)-6-fluoro-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-ylmethylidene)-6-fluoro-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-ylmethylidene)-6-fluoro-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-ylmethylidene)-6-fluoro-2-indolinone			
3-[3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-ylmethylidene]-6-fluoro-2-indolinone			
3-[3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-ylmethylidene]-6-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-ylmethylidene)-5-bromo-4-methyl-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-ylmethylidene)-5-bromo-4-methyl-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-ylmethylidene)-5-bromo-4-methyl-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-ylmethylidene)-5-bromo-4-methyl-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-ylmethylidene)-5-bromo-4-methyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-ylmethylidene)-5-bromo-4-methyl-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-ylmethylidene)-5-bromo-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-ylmethylidene)-5-bromo-4-methyl-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-ylmethylidene)-5-bromo-4-methyl-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-ylmethylidene)-5-bromo-4-methyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-ylmethylidene)-7-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-ylmethylidene)-7-fluoro-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene)-7-fluoro-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene)-7-fluoro-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene)-7-fluoro-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene)-7-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene)-7-fluoro-2-indolinone			
3-[3-(4-methylphenyl-4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene)-7-fluoro-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene)-7-fluoro-2-indolinone			
3-[3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene]-7-fluoro-2-indolinone			
3-[3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene]-7-fluoro-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene)-7-fluoro-2-indolinone			
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-ylmethylidene)-7-fluoro-2-indolinone			

3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-7-fluoro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-7-fluoro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-7-fluoro-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone					
3-[3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl]-7-fluoro-2-indolinone					
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone					
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-7-fluoro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-fluoro-2-indolinone					
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-fluoro-2-indolinone					
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-fluoro-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-fluoro-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-fluoro-2-indolinone					
3-[3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-7-fluoro-2-indolinone					
3-[3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-7-fluoro-2-indolinone					
3-[3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-7-fluoro-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone					
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone					
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone					
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone					
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone					
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone					
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-bromo-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-bromo-4-methyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-4-methyl-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-4-methyl-2-indolinone					
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-4-methyl-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-4-methyl-2-indolinone					



3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-[3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-bromo-4-methyl-2-indolinone			
3-(3-phenylsulfonylmethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-[3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-[3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-[3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl]-5-bromo-4-methyl-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-[3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-bromo-4-methyl-2-indolinone			
3-[3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-bromo-4-methyl-2-indolinone			
3-[3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-bromo-4-methyl-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-4-methyl-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-methyl-2-indolinone			

3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-methyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-methyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-methyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methyl-2-indolinone				
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-methyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-methyl-2-indolinone				
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone				
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone				

3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			

3-[3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-chloro-7-methyl-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-7-methyl-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-nitro-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-nitro-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-nitro-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-nitro-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-nitro-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-nitro-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-iodo-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-2-indolinone			
3-[3-(4-methylphenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-2-indolinone			
3-[3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-iodo-2-indolinone			
3-[3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-iodo-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-phenylaminoethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-iodo-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-iodo-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone			
3-[3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl]-5-iodo-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone			

3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-2-indolinone					
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-2-indolinone					
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-2-indolinone					
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-2-indolinone					
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-2-indolinone					
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-2-indolinone					
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-iodo-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-iodo-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone					
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-iodo-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone					
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone					
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone					
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-nitro-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-nitro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-nitro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-nitro-2-indolinone					

[illegible]

3-[3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-5-fluoro-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone			
3-[3-(isouinol-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl]-5-fluoro-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-fluoro-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-fluoro-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-fluoro-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-fluoro-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-fluoro-2-indolinone			
3-[3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-fluoro-2-indolinone			
3-[3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-fluoro-2-indolinone			
3-[3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-5-fluoro-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-fluoro-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			

3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-[3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-7-bromo-5-chloro-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-[3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-7-bromo-5-chloro-2-indolinone			
3-[3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-7-bromo-5-chloro-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-[3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl]-7-bromo-5-chloro-2-indolinone			
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-[3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-7-bromo-5-chloro-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-7-bromo-5-chloro-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone			



[illegible]

3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5,7-dibromo-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-2-indolinone					
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-2-indolinone					
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-2-indolinone					
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-2-indolinone					
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5,7-dibromo-2-indolinone					
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-(isouquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4-methyl-2-indolinone					
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4-methyl-2-indolinone					

3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4-methyl-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4-methyl-2-indolinone				
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4-methyl-2-indolinone				
3-[3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-4-methyl-2-indolinone				
3-[3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl]-4-methyl-2-indolinone				
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4-methyl-2-indolinone				
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4-methyl-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-4-methyl-2-indolinone				
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone				
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone				
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone				
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone				
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-4-methyl-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-2-indolinone				
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-2-indolinone				
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-2-indolinone				
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-2-indolinone				
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-2-indolinone				
3-[3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-2-indolinone				
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-2-indolinone				
3-[3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-2-indolinone				
3-[3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl]-2-indolinone				
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-2-indolinone				
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-2-indolinone				
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-[3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl]-2-indolinone				

3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-2-indolinone				
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-2-indolinone				
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-2-indolinone				
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-2-indolinone				
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-2-indolinone				
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-2-indolinone				
3-(3-(2-methylaminoethoxy)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-2-indolinone				
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-2-indolinone				
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(3-(4-methylphenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5,6-dimethoxy-2-indolinone				

[illegible]

3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					

3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-4,6-dimethyl-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-chloro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-chloro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone					
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-2-indolinone					
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-chloro-2-indolinone					
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-chloro-2-indolinone					
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone					

3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone				
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone				
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone				
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone				
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone				
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-chloro-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-4,5-dimethyl-2-indolinone				
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-bromo-2-indolinone				
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-(isochinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-2-indolinone				



3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-2-indolinone			
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-2-indolinone			
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-2-indolinone			
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-2-indolinone			
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-bromo-2-indolinone			
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-bromo-2-indolinone			
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone			
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone			
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone			
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone			
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone			
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone			
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone			
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-bromo-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-chloro-2-indolinone			
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-chloro-2-indolinone			
3-(3-n-pentyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(3-ethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(3-(4-methylphenyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(3-phenylsulfonylmethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(3-(1-phenylaminoethyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(3-(1-phenylaminobutyl)-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(3-cyano-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(3-phenylaminomethyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(3-phenyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-amino-2-indolinone			
3-(4,5,6,7-tetrahydrobenzimidazol-2-methylidenyl)-5-amino-2-indolinone			
3-(4,5,6,7-tetrahydrobenzoxazol-2-methylidenyl)-5-amino-2-indolinone			
3-(3-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone			
3-(3-carboxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone			
3-(3-(isoquinolin-1-methyl)-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone			

3-(3-hydroxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(3-methoxy-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-amino-2-indolinone				
3-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-amino-2-indolinone				
3-(3-vinyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-amino-2-indolinone				
3-(3-carboxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-amino-2-indolinone				
3-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-amino-2-indolinone				
3-(3-(3-dimethylamino-n-propoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-amino-2-indolinone				
3-(3-(3-diethylaminoethoxycarbonyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-amino-2-indolinone				
3-(3-(2-methylaminoethyl)-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-amino-2-indolinone				
3-(3-cyclopropylmethoxy-4,5,6,7-tetrahydrobenzothien-2-methylidenyl)-5-amino-2-indolinone				
3-(4,5,6,7-tetrahydrobenzothiazol-2-methylidenyl)-5-amino-2-indolinone				
3-(4-methyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(4,4-dimethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(4-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(4-phenyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(3-ethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(3-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(4-isopropyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(4-carboxymethyl-4,5,6,7-tetrahydroindol-2-methylidenyl)-5-amino-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydroinden-2-methylidenyl)-5-bromo-2-indolinone				
3-(4,5,6,7-tetrahydroinden-2-methylidenyl)-5-bromo-2-indolinone				
3-(3-methyl-4,5,6,7-tetrahydrobenzofuran-2-methylidenyl)-5-bromo-2-indolinone				

## 2. The Biochemistry

In yet another embodiment, this invention relates to a method for the modulation of the catalytic activity of PKs by contacting a PK with a compound of this invention or a  
5 physiologically acceptable salt or prodrug thereof.

By "PK" is meant RTKs, CTKs and STKs; i.e., the modulation of RTK, CTK and STK catalyzed signaling processes are contemplated by this invention.

The term "method" refers to manners, means, techniques  
10 and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by, practitioners of the chemical, pharmacological, biological, biochemical  
15 and medical arts.

As used herein, the term "modulation" or "modulating" refers to the alteration of the catalytic activity of RTKs, CTKs and STKs. In particular, modulating refers to the activation of the catalytic activity of RTKs, CTKs and STKs,  
20 preferably the activation or inhibition of the catalytic activity of RTKs, CTKs and STKs, depending on the concentration of the compound or salt to which the RTK, CTK or STK is exposed or, more preferably, the inhibition of the catalytic activity of RTKs, CTKs and STKs.

25 The term "catalytic activity" as used herein refers to the rate of phosphorylation of tyrosine under the influence, direct or indirect of RTKs and/or CTKs or the phosphorylation of serine and threonine under the influence, direct or indirect, of STKs.

30 The term "contacting" as used herein refers to bringing a compound of this invention and a target PK together in

such a manner that the compound can affect the catalytic activity of the PK, either directly; i.e., by interacting with the kinase itself, or indirectly; i.e., by interacting with another molecule on which the catalytic activity of the kinase is dependent. Such "contacting" can be accomplished in a test tube, a petri dish or the like. In a test tube, contacting may involve only a compound and a PK of interest or it may involve whole cells. Cell may also be maintained or grown in cell culture dishes and contacted with the compound in that environment. In this context, the ability of a particular compound to affect a PK related disorder; i.e., the IC50 of the compound, defined below, can be determined before the compounds are used in vivo with more complex living organisms is attempted. For cells outside the organism, multiple methods exist, and are well-known to those skilled in the arts, to get the PKs in contact with the compounds including, but not limited to, direct cell microinjection and numerous transmembrane carrier techniques.

RTK mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization, transient stimulation of the intrinsic protein tyrosine kinase activity and phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic effects to the extracellular micro-environment). See, Schlessinger and Ullrich, 1992, Neuron 9:303-391.

It has been shown that tyrosine phosphorylation sites in growth factor receptors function as high-affinity binding

sites for SH2 (src homology) domains of signaling molecules. Fantl et al., 1992, Cell 69:413-423; Songyang et al., 1994, Mol. Cell. Biol. 14:2777-2785; Songyang et al., 1993, Cell 72:767-778; and Koch et al., 1991, Science 252:668-678.

5 Several intracellular substrate proteins that associate with RTKs have been identified. They may be divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack such domain but serve as adapters and associate with catalytically active  
10 molecules. Songyang et al., 1993, Cell 72:767-778. The specificity of the interactions between receptors and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in the binding affinities between SH2  
15 domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate phosphorylation profiles. Songyang et al., 1993, Cell 72:767-778. These observations suggest that the function of  
20 each RTK is determined not only by its pattern of expression and ligand availability but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step which determines the selectivity  
25 of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

STKs, being primarily cytosolic, affect the internal biochemistry of the cell often as a down-line response to a PTK event. STKs have been implicated in the signaling  
30 process which initiates DNA synthesis and subsequent mitosis leading to cell proliferation.

Thus, PK signal transduction results in, among other responses, cell proliferation, differentiation, growth and metabolism. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis).

A precise understanding of the mechanism by which the compounds of this invention inhibit PKs is not required in order to practice the present invention. However, while not hereby being bound to any particular mechanism or theory, it is believed that the compounds interact with the amino acids of the catalytic region of PKs. PKs typically possess a bilobate structure wherein ATP appears to bind in the cleft between the two lobes in a region where the amino acids are conserved among PKs. Inhibitors of PKs are believed to bind by non-covalent interactions such as hydrogen bonding, van der Waals forces and ionic interactions in the same general region where the aforesaid ATP binds to the PKs. More specifically, it is thought that the 2-indolinone component of the compounds of this invention binds in the general space normally occupied by the adenine ring of ATP. Specificity of a particular molecule for a particular PK could arise as the result of additional interactions between the various substituents on the 2-indolinone core with amino acid domains specific to particular PKs. Thus, different indolinone substituents may contribute to preferential binding to particular PKs. The ability to select those compounds active at different ATP (or other nucleotide) binding sites makes the compounds useful for targeting any protein with such a site; i.e., not only PKs but protein

phosphatases as well. The compounds disclosed herein thus have utility for in vitro assays on such proteins and for in vivo therapeutic effects through such proteins.

In another aspect, the protein kinase, the catalytic activity of which is modulated by contact with a compound of this invention, is a protein tyrosine kinase, more particularly, a receptor protein tyrosine kinase. Among the receptor protein tyrosine kinases whose catalytic activity can be modulated with a compound of this invention, or salt thereof, are, without limitation, EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFR $\alpha$ , PDGFR $\beta$ , CSF1R, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R and FGFR-4R.

The protein tyrosine kinase whose catalytic activity is modulated by contact with a compound of this invention, or a salt or a prodrug thereof, can also be a non-receptor or cellular protein tyrosine kinase (CTK). Thus, the catalytic activity of CTKs such as, without limitation, Src, Frk, Btk, Csk, Abl, ZAP70, Fes/Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk, may be modulated by contact with a compound or salt of this invention.

Still another group of PKs which may have their catalytic activity modulated by contact with a compound of this invention are the serine-threonine protein kinases such as, without limitation, CDK2 and Raf.

In another aspect, this invention relates to a method for treating or preventing a PK related disorder by administering a therapeutically effective amount of a pharmacological composition of this compound of this invention or a salt or a prodrug thereof to an organism.

As used herein, "PK related disorder," "PK driven disorder," and "abnormal PK activity" all refer to a condi-

tion characterized by inappropriate; i.e., under or, more commonly, over, PK catalytic activity, where the particular PK be an RTK, a CTK or an STK. Inappropriate catalytic activity can arise as the result of either: (1) PK expression in cells which normally do not express PKs; (2) increased PK expression leading to unwanted cell proliferation, differentiation and/or growth; or, (3) decreased PK expression leading to unwanted reductions in cell proliferation, differentiation and/or growth. Over-activity of PKs refers to either amplification of the gene encoding a particular PK or production of a level of PK activity which can correlate with a cell proliferation, differentiation and/or growth disorder (that is, as the level of the PK increases, the severity of one or more of the symptoms of the cellular disorder increases). Underactivity is, of course, the converse, wherein the severity of one or more symptoms of a cellular disorder increase as the level of the PK decreases.

As used herein, the terms "prevent", "preventing" and "prevention" refer to a method for barring an organism from in the first place acquiring an PK mediated cellular disorder.

As used herein, the terms "treat", "treating" and "treatment" refer to a method of alleviating or abrogating the PK mediated cellular disorder and/or its attendant symptoms. With regard particularly to cancer, these terms simply mean that the life expectancy of an individual affected with a cancer will be increased or that one or more of the symptoms of the disease will be reduced.

The term "organism" refers to any living entity comprised of at least one cell. A living organism can be as



simple as, for example, a single eukariotic cell or as complex as a mammal, including a human being.

The term "therapeutically effective amount" as used herein refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of cancer, a therapeutically effective amount refers to that amount which has the effect of (1) reducing the size of the tumor; (2) inhibiting (that is, slowing to some extent, preferably stopping) tumor metastasis; (3) inhibiting to some extent (that is slowing to some extent, preferably stopping) tumor growth; and/or, (4) relieving to some extent (or preferably eliminating) one or more symptoms associated with the cancer.

This invention is therefore directed to compounds which modulate PK signal transduction by affecting the enzymatic activity of the RTKs, CTKs and/or STKs and thereby interfering with the signal transduced by such proteins. More particularly, the present invention is directed to compounds which modulate the RTK, CTK and/or STK mediated signal transduction pathways as a therapeutic approach to cure many kinds of solid tumors, including but not limited to carcinoma, sarcomas including Kaposi's sarcoma, leukemia, erythroblastoma, glioblastoma, meningioma, astrocytoma, melanoma and myoblastoma. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers, pancreas cancers, colon cancers, blood cancers, lung cancers, bone cancers and leukemias.

Further examples, without limitation, of the types of disorders related to unregulated PK activity that the compounds described herein may be useful in preventing,

treating and studying, are cell proliferative disorders, fibrotic disorders and metabolic disorders.

Cell proliferative disorders, which may be prevented, treated or further studied by the present invention include  
5 cancers, blood vessel proliferative disorders and mesangial cell proliferative disorders.

Blood vessel proliferative disorders refer to angiogenic and vasculogenic disorders generally resulting in abnormal proliferation of blood vessels. The formation and  
10 spreading of blood vessels, or vasculogenesis and angiogenesis, respectively, play important roles in a variety of physiological processes such as embryonic development, corpus luteum formation, wound healing and organ regeneration. They also play a pivotal role in cancer development.  
15 Other examples of blood vessel proliferation disorders include arthritis, where new capillary blood vessels invade the joint and destroy cartilage, and ocular diseases, like diabetic retinopathy, where new capillaries in the retina invade the vitreous, bleed and cause blindness. Conversely,  
20 disorders related to the shrinkage, contraction or closing of blood vessels, such as restenosis, are also implicated.

Fibrotic disorders refer to the abnormal formation of extracellular matrices. Examples of fibrotic disorders include hepatic cirrhosis and mesangial cell proliferative  
25 disorders. Hepatic cirrhosis is characterized by the increase in extracellular matrix constituents resulting in the formation of a hepatic scar. Hepatic cirrhosis can cause diseases such as cirrhosis of the liver. An increased extracellular matrix resulting in a hepatic scar can also be  
30 caused by viral infection such as hepatitis. Lipocytes appear to play a major role in hepatic cirrhosis. Other fibrotic disorders implicated include atherosclerosis.

Mesangial cell proliferative disorders refer to disorders brought about by abnormal proliferation of mesangial cells. Mesangial proliferative disorders include various human renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, and glomerulopathies. The PDGF-R has been implicated in the maintenance of mesangial cell proliferation. Floege et al., 1993, Kidney International 43:47S-54S.

As noted previously, PKs have been associated with such cell proliferative disorders. For example, some members of the RTK family have been associated with the development of cancer. Some of these receptors, like the EGFR (Tuzi et al., 1991, Br. J. Cancer 63:227-233; Torp et al., 1992, APMIS 100:713-719) HER2/neu (Slamon et al., 1989, Science 244:707-712) and the PDGF-R (Kumabe et al., 1992, Oncogene, 7:627-633) are over-expressed in many tumors and/or persistently activated by autocrine loops. In fact, in the most common and severe cancers these receptor over-expressions (Akbasak and Suner-Akbasak et al., 1992, J. Neurol. Sci., 111:119-133; Dickson et al., 1992, Cancer Treatment Res. 61:249-273; Korc et al., 1992, J. Clin. Invest. 90:1352-1360) and autocrine loops (Lee and Donoghue, 1992, J. Cell. Biol., 118:1057-1070; Korc et al., supra; Akbasak and Suner-Akbasak et al., supra) have been demonstrated. For example, the EGFR receptor has been associated with squamous cell carcinoma, astrocytoma, glioblastoma, head and neck cancer, lung cancer and bladder cancer. HER2 has been associated with breast, ovarian, gastric, lung, pancreas and bladder cancer. PDGFR has been associated with glioblastoma, lung, ovarian, melanoma and prostate. The RTK c-met has been generally associated with hepatocarcino-

genesis and thus hepatocellular carcinoma. C-met has been linked to malignant tumor formation. More specifically, the RTK c-met has been associated with, among other cancers, colorectal, thyroid, pancreatic and gastric carcinoma, leukemia and lymphoma. Additionally, over-expression of the c-met gene has been detected in patients with Hodgkins disease, Burkitts disease, and the lymphoma cell line.

Flk has been associated with a broad spectrum of tumors including without limitation mammary, ovarian and lung tumors as well as gliomas such as glioblastoma.

IGF-IR, in addition to being implicated in nutritional support and in type-II diabetes, has also been associated with several types of cancers. For example, IGF-I has been implicated as an autocrine growth stimulator for several tumor types, e.g. human breast cancer carcinoma cells (Arteaga et al., 1989, J. Clin. Invest. 84:1418-1423) and small lung tumor cells (Macauley et al., 1990, Cancer Res., 50:2511-2517). In addition, IGF-I, integrally involved in the normal growth and differentiation of the nervous system, appears to be an autocrine stimulator of human gliomas. Sandberg-Nordqvist et al., 1993, Cancer Res. 53:2475-2478. The importance of the IGF-IR and its ligands in cell proliferation is further supported by the fact that many cell types in culture (fibroblasts, epithelial cells, smooth muscle cells, T-lymphocytes, myeloid cells, chondrocytes, osteoblasts, the stem cells of the bone marrow) are stimulated to grow by IGF-I. Goldring and Goldring, 1991, Eukaryotic Gene Expression, 1:301-326. In a series of recent publications, Baserga even suggests that IGF-IR plays a central role in the mechanisms of transformation and, as such, could be a preferred target for therapeutic interventions for a broad spectrum of human malignancies.

Baserga, 1995, Cancer Res., 55:249-252; Baserga, 1994, Cell 79:927-930; Coppola et al., 1994, Mol. Cell. Biol., 14:4588-4595.

STKs have been implicated in many types of cancer including notably breast cancer (Cance, et al., Int. J. Cancer, 54:571-77 (1993)).

The association between abnormal PK activity and disease are not restricted to cancer, however. For example, RTKs have been associated with diseases such as psoriasis, diabetes mellitus, endometriosis, angiogenesis, atheromatous plaque development, Alzheimer's disease, epidermal hyperproliferation and neurodegenerative diseases age-related macular degeneration, hemangiomas. For example, the EGF-R is indicated in corneal and dermal wound healing. Defects in the Insulin-R and the IGF-1R are indicated in type-II diabetes mellitus. A more complete correlation between specific RTKs and their therapeutic indications is set forth in Plowman et al., 1994, DN&P 7:334-339.

As noted previously, not only RTKs but CTKs as well including, but not limited to, src, abl, fps, yes, fyn, lyn, lck, blk, hck, fgr and yrk (reviewed by Bolen et al., 1992, FASEB J., 6:3403-3409) are involved in the proliferative and metabolic signal transduction pathway and thus were expected, and have been shown, to be involved in many PTK-mediated disorders to which the present invention is directed. For example, mutated src (v-src) has been demonstrated as an oncoprotein (pp60<sup>v-src</sup>) in chicken. Moreover, its cellular homolog, the proto-oncogene pp60<sup>c-src</sup>, transmits oncogenic signals of many receptors. For example, over-expression of EGFR or HER2/neu in tumors leads to the constitutive activation of pp60<sup>c-src</sup>, which is characteristic for the malignant cell but absent from the normal cell. On

the other hand, mice deficient in the expression of c-src exhibit an osteopetrotic phenotype, indicating a key participation of c-src in osteoclast function and a possible involvement in related disorders. Similarly, Zap70 is implicated in T-cell signaling.

STKs have been associated with inflammation, autoimmune disease, immunoresponses, and hyperproliferation disorders such as restinosis, fibrosis, psoriasis, osteoarthritis and rheumatoid arthritis.

PKs have also been implicated in embryo implantation and the compounds of this invention may provide an effective method of preventing embryo implantation.

Finally, both RTKs and CTKs are currently suspected as being involved in hyperimmune disorders.

### 3. Pharmacological Compositions And Therapeutic Applications

A compound of the present invention, a prodrug thereof or its physiologically acceptable salt of either the salt or prodrug can be administered as such to a human patient or in pharmacological compositions where these are mixed with suitable carriers or excipient(s). Techniques for formulation and administration of drugs may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition.

#### A. Routes of Administration.

As used herein, "administer" or "administration" refers to the delivery of a compound, salt or prodrug of the present invention or of a pharmacological composition containing a compound, salt or prodrug of this invention to an organism for the purpose of prevention or treatment of a PK-related disorder.

Suitable routes of administration may include, without limitation, oral, rectal, transmucosal or intestinal administration; or, intramuscular, subcutaneous, intramedullary, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a solid tumor, often in a depot or sustained release formulation.

Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will be targeted to and taken up selectively by the tumor.

#### Composition/Formulation

Pharmacological compositions of the present invention may be manufactured by processes well known in the art; e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmacological compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the

barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmacological preparations for oral use can be made with the use of a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.



Pharmacological compositions which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in

multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or  
5 dispersing agents.

Pharmacological compositions for parenteral administration include aqueous solutions of the active compounds in water soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection  
10 suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension,  
15 such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

20 Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas,  
25 e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by  
30 implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or

hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

5       The pharmacological compositions herein also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and  
10       polymers such as polyethylene glycols.

Many of the PK modulating compounds of the invention may be provided as physiologically acceptable salts wherein the claimed compound may form the negatively or the positively charged species. Examples of salts in which the  
15       compound forms the positively charged moiety include, without limitation, quaternary ammonium (defined elsewhere herein), salts such as the hydrochloride, sulfate, carbonate, lactate, tartrate, maleate, succinate, etc. formed by the reaction of an amino group with the appropriate acid.  
20       Salts in which the compound forms the negatively charged species include, without limitation, the sodium, potassium, calcium and magnesium salts formed by the reaction of a carboxylic acid group in the molecule with the appropriate base (e.g. sodium hydroxide (NaOH), potassium hydroxide  
25       (KOH), Calcium hydroxide (Ca(OH)<sub>2</sub>), etc.).

#### C. Dosage.

Pharmacological compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount effective to achieve  
30       its intended purpose.

More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

5 Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any compound used in the methods of the invention,  
10 the therapeutically effective amount or dose can be estimated initially from cell culture assays. Then, the dosage can be formulated for use in animal models so as to achieve a circulating concentration range that includes the  $IC_{50}$  as determined in cell culture (i.e., the concentration of the  
15 test compound which achieves a half-maximal inhibition of the PK activity). Such information can then be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental  
20 animals, e.g., for determining the  $LD_{50}$  (the dose lethal to 50% of the population) and the  $ED_{50}$  (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and  
25 it can be expressed as the ratio between  $LD_{50}$  and  $ED_{50}$ . Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies  
30 preferably within a range of circulating concentrations that include the  $ED_{50}$  with little or no toxicity. The dosage may vary within this range depending upon the dosage form

employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the kinase modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data; e.g., the concentration necessary to achieve 50-90% inhibition of the kinase using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

D. Packaging.

The compositions may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or human or veterinary administration. Such notice, for example, may be of the labeling approved by the U.S. Foods and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Suitable conditions indicated on the label may include treatment of a tumor, inhibition of angiogenesis, treatment of fibrosis, diabetes, and the like.

4. Synthesis

The compounds of this invention, as well as the precursor 2-oxindoles and aldehydes, may be readily synthesized using techniques well known in the chemical arts. It will be appreciated by those skilled in the art that other synthetic pathways for forming the compounds of the invention are available and that the following is offered by way of example and not limitation.

A. General synthetic procedure.

The following general methodology may be employed to prepare the compounds of this invention:

The appropriately substituted 2-oxindole (1 equiv.),  
5 the appropriately substituted aldehyde (1.2 equiv.) and piperidine (0.1 equiv.) are mixed with ethanol (1-2 ml/mmol 2-oxindole) and the mixture is then heated at 90° C for 3 to 5 hours. After cooling, the reaction mixture is concentrated and acidified to pH 3. The precipitate which forms is  
10 filtered, washed with water to pH 7 and then cold ethanol, ethyl acetate and/or hexane and vacuum dried to yield the target compound. The product may optionally be further purified by chromatography.

B. 2-oxindoles

15 The following examples show representative syntheses of several of the 2-oxindole precursors to the compounds of this invention. These 2-oxindoles, as well as the others claimed, will form the claimed compounds by reaction with an appropriately substituted aldehyde under the conditions  
20 described above. It is to be understood that the following syntheses are provided by way of example only and are not to be construed as limiting as to synthetic procedure or as to the compounds described.

5-Amino-2-oxindole

25 5-Nitro-2-oxindole (6.3 g) was hydrogenated in methanol over 10% palladium on carbon to give 3.0 g (60% yield) of the title compound as a white solid.

5-Bromo-2-oxindole

30 2-Oxindole (1.3 g) in 20 mL acetonitrile was cooled to -10°C and 2.0 g N-bromosuccinimide was slowly added with

stirring. The reaction was stirred for 1 hour at  $-10^{\circ}\text{C}$  and 2 hours at  $0^{\circ}\text{C}$ . The precipitate was collected, washed with water and dried to give 1.9 g (90% yield) of the title compound.

5    4-Methyl-2-oxindole

Diethyl oxalate (30 mL) in 20 mL of dry ether was added with stirring to 19 g of potassium ethoxide suspended in 50 mL of dry ether. The mixture was cooled in an ice bath and 20 mL of 3-nitro-o-xylene in 20 mL of dry ether was slowly  
10    added. The thick dark red mixture was heated to reflux for 0.5 hr, concentrated to a dark red solid, and treated with 10% sodium hydroxide until almost all of the solid dissolved. The dark red mixture was treated with 30% hydrogen peroxide until the red color changed to yellow. The  
15    mixture was treated alternately with 10% sodium hydroxide and 30% hydrogen peroxide until the dark red color was no longer present. The solid was filtered off and the filtrate acidified with 6N hydrochloric acid. The resulting precipitate was collected by vacuum filtration, washed with  
20    water, and dried under vacuum to give 9.8 g (45% yield) of 2-methyl-6-nitrophenylacetic acid as an off-white solid. The solid was hydrogenated in methanol over 10% palladium on carbon to give 9.04 g of the title compound as a white solid.

25    7-Bromo-5-chloro-2-oxindole

5-Chloro-2-oxindole (16.8 g) and 19.6 g of N-bromosuccinimide were suspended in 140 mL of acetonitrile and refluxed for 3 hours. Thin layer chromatography (silica, ethyl acetate) at 2 hours of reflux showed 5-chloro-2-  
30    oxindole or N-bromosuccinimide ( $R_f$  0.8), product ( $R_f$  0.85) and a second product ( $R_f$  0.9) whose proportions did not



change after another hour of reflux. The mixture was cooled to 10°C, the precipitate was collected by vacuum filtration, washed with 25 mL of ethanol and sucked dry for 20 minutes in the funnel to give 14.1 g of wet product (56% yield). The solid was suspended in 200 mL of denatured ethanol and slurry-washed by stirring and refluxing for 10 minutes. The mixture was cooled in an ice bath to 10°C. The solid product was collected by vacuum filtration, washed with 25 mL of ethanol and dried under vacuum at 40°C to give 12.7 g (51% yield) of 7-bromo-5-chloro-2-oxindole.

#### 5-Fluoro-2-oxindole

5-Fluoroisatin (8.2 g) was dissolved in 50 mL of hydrazine hydrate and refluxed for 1.0 hr. The reaction mixtures were then poured in ice water. The precipitate was then filtered, washed with water and dried under vacuum oven afford the title compound.

#### 5-Nitro-2-oxindole

2-Oxindole (6.5 g) was dissolved in 25 mL concentrated sulfuric acid and the mixture maintained at -10 to -15°C while 2.1 mL of fuming nitric acid was added dropwise. After the addition of the nitric acid the reaction mixture was stirred at 0°C for 0.5 hr and poured into ice-water. The precipitate was collected by filtration, washed with water and crystallized from 50% acetic acid. The crystalline product was then filtered, washed with water and dried under vacuum to give 6.3 g (70%) of 5-nitro-2-oxindole.

#### 5-Iodo-2-oxindole

2-Oxindole (82.9 g) was suspended in 630 mL of acetic acid with mechanical stirring and the mixture cooled to 10°C in an ice water bath. Solid N-iodosuccinimide (175 g) was

added in portions over 10 minutes. After the addition was complete the mixture was stirred for 1.0 hour at 10°C. The suspended solid which had always present became very thick at this time. The solid was collected by vacuum filtration, washed with 100 mL of 50% acetic acid in water and then with 200 mL of water and sucked dry for 20 minutes in the funnel. The product was dried under vacuum to give 93.5 g (36%) of 5-iodo-2-oxindole containing about 5% 2-oxindole by proton NMR.

10 5-Methyl-2-oxindole

5-Methylisatin (15.0 g) and 60 mL of hydrazine hydrate were heated at 140 to 160°C for 4 hours. Thin layer chromatography (ethyl acetate:hexane 1:2, silica gel) showed no starting material remaining. The reaction mixture was cooled to room temperature, poured into 300 mL of ice water and acidified to pH 2 with 6N hydrochloric acid. After standing at room temperature for 2 days the precipitate was collected by vacuum filtration, washed with water and dried under vacuum to give 6.5 g (47% yield) of 5-methyl-2-oxindole.

5-Bromo-4-methyloxindole and 5,7-Dibromo-4-methyloxindole

4-Methyl-2-oxindole (5 g) in 40 mL of acetonitrile was treated with 7.26 g of N-bromosuccinimide and stirred at room temperature for 4 hours. Thin layer chromatography (ethyl acetate:hexane 1:2, silica gel) showed a mixture of 5-bromo (Rf 0.3) and 5,7-dibromo (Rf 0.5) products. Another 7.26 g of N-bromosuccinimide was added and the mixture stirred for 4 additional hours. The solid was collected by vacuum filtration, washed with 20 mL of acetonitrile and dried to give a 1: 1 mixture of mono and dibromo compounds. The filtrate was concentrated and chromatographed on silica

gel (ethyl acetate:hexane (1:2)) to give 1.67 g of 5-bromo-4-methyl-2-oxindole as a beige solid. The remaining 1:1 mixture of solids was recrystallized twice from glacial acetic acid to give 3.2 g of 5,7-dibromo-4-methyl-2-oxindole as a light orange solid. The filtrates from this material were chromatographed as above to give 0.6 g of 5-bromo-4-methyl-2-oxindole and 0.5 g of 5,7-dibromo-4-methyl-2-oxindole.

#### 6-Fluoro-2-oxindole

10 Sodium hydride (2.6 g) and 14.5 g of dimethylmalonate was stirred and heated to 100°C in 160 mL dimethylsulfoxide for 1.0 hour. The mixture was cooled to room temperature, 7.95 g of 2,5-difluoronitrobenzene were added and mixture stirred for 30 minutes. The mixture was then heated to 100°C  
15 for 1.0 hour, cooled to room temperature and poured into 400 mL of saturated ammonium chloride solution. The mixture was extracted with 200 mL of ethyl acetate and the organic layer washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was crystallized from  
20 methanol to give 24.4 g (80% yield) of dimethyl 4-fluoro-2-nitrophenylmalonate as a white solid, R<sub>f</sub> 0.2 on thin layer chromatography (ethyl acetate:hexane 1:6, silica gel). The filtrate was concentrated and chromatographed on a column of silica gel (ethyl acetate:hexane 1:8) to give an  
25 additional 5.03 g of dimethyl 4-fluoro-2-nitrophenylmalonate, for a total of 29.5 g (96% yield).

Dimethyl 4-fluoro-2-nitrophenylmalonate (5.0 g) was refluxed in 20 mL of 6N hydrochloric acid for 24 hours. The reaction was cooled and the white solid collected by vacuum  
30 filtration, washed with water and dried to give 3.3 g (87%

yield) of 4-fluoro-2-nitrophenylacetic acid, Rf 0.6 on thin layer chromatography (ethyl acetate:hexane 1:2, silica gel).

4-Fluoro-2-nitrophenylacetic acid (3.3 g) dissolved in 15 mL of acetic acid was hydrogenated over 0.45 g of 10% palladium on carbon at 60 psi H<sub>2</sub> for 2 hours. The catalyst was removed by filtration and washed with 15 mL of methanol. The combined filtrates were concentrated and diluted with water. The precipitate was collected by vacuum filtration, washed with water and dried to give 1.6 g (70% yield) of 6-fluoro-2-oxindole, Rf 0.24 on thin layer chromatography. The filtrate was concentrated to give a purple solid with an NNM spectrum similar to the first crop. Chromatography of the purple solid (ethyl acetate:hexane 1:2, silica gel) gave a second crop of 6-fluoro-2-oxindole as a white solid.

15 5-Aminosulfonyl-2-oxindole

To a 100 mL flask charged with 27 mL of chlorosulfonic acid was added slowly 13.3 g of 2-oxindole. The reaction temperature was maintained below 30°C during the addition. After the addition, the reaction mixture was stirred at room temperature for 1.5 hr, heated to 68°C for 1 hr, cooled, and poured into water. The precipitate was washed with water and dried in a vacuum oven to give 11.0 g of 5-chlorosulfonyl-2-oxindole (50% yield) which was used without further purification.

25 5-Chlorosulfonyl-2-oxindole (2.1 g) was added to 10 mL of ammonium hydroxide in 10 mL of ethanol and stirred at room temperature overnight. The mixture was concentrated and the solid collected by vacuum filtration to give 0.4 g (20% yield) of the title compound as an off-white solid.

5-Methylaminosulfonyl-2-oxindole

A suspension of 3.38 g of 5-chlorosulfonyl-2-oxindole in 10 mL 2M methylamine in tetrahydrofuran was stirred at room temperature for 4 hours during which time a white solid  
5 formed. The precipitate was collected by vacuum filtration, washed twice with 5 mL of water and dried under vacuum at 40°C overnight to give 3.0 g (88% yield) of 5-methylamino-sulfonyl-2-oxindole.

5-(4-Trifluoromethylphenylaminosulfonyl)-2-oxindole

10 A suspension of 2.1 g of 5-chlorosulfonyl-2-oxindole, 1.6 g of 4-trifluoromethylaniline and 1.4 g of pyridine in 20 mL of dichloromethane was stirred at room temperature for 4 hours. The precipitate which formed was collected by vacuum filtration, washed twice with 5 mL of water and dried  
15 under vacuum at 40°C overnight to give 2.4 g of crude product containing some impurities by thin layer chromatography. The crude product was chromatographed on silica gel eluting with ethyl acetate:hexane (1:2) to give 1.2 g (37% yield) of 5-(4-trifluoromethylphenyl-  
20 aminosulfonyl)-2-oxindole.

5-(Morpholinosulfonyl)-2-oxindole

A suspension of 2.3 g of 5-chlorosulfonyl-2-oxindole and 2.2 g of morpholine in 50 mL of dichloromethane was stirred at room temperature for 3 hours. The white  
25 precipitate was collected by vacuum filtration, washed with ethyl acetate and hexane and dried under vacuum at 40°C overnight to give 2.1 g (74% yield) of 5-(morpholinosulfonyl)-2-oxindole.

6-Trifluoromethyl-2-oxindole

Dimethylsulfoxide (330 mL) was added to 7.9 g of sodium hydride followed by dropwise addition of 43.6 g diethyloxalate. The mixture was heated to 100°C for 1.0 hour and cooled to room temperature. 2-Nitro-4-trifluoromethyl-toluene (31.3 g) was added, the reaction stirred for 30 minutes at room temperature and then heated to 100°C for 1 hour. The reaction was cooled and poured into a mixture of saturated aqueous ammonium chloride, ethyl acetate and hexane. The organic layer was washed with saturated ammonium chloride, water and brine, dried, and concentrated to give dimethyl 2-(2-nitro-4-trifluoromethylphenyl)malonate.

The diester was dissolved in a mixture of 6.4 g of lithium chloride and 2.7 mL of water in 100 mL of dimethylsulfoxide and heated to 100°C for 3 hours. The reaction was cooled and poured into a mixture of ethyl acetate and brine. The organic phase was washed with brine, dried with sodium sulfate, concentrated and chromatographed on silica gel (10% ethyl acetate in hexane). The fractions containing product were evaporated to give 25.7 g of methyl 2-nitro-4-trifluoromethylphenylacetate.

Methyl 2-nitro-4-trifluoromethylphenylacetate (26 mg) was hydrogenated over 10% palladium on carbon and then heated at 100°C for 3 hours. The catalyst was removed by filtration and the solvent evaporated to give the title compound.

5-(2-Chloroethyl)oxindole

5-Chloroacetyl-2-oxindole (4.18 g) in 30 mL of trifluoroacetic acid in an ice bath was treated with 4.65 g of triethylsilane and stirred at room temperature for 3 hours. The mixture was poured into 150 mL of water and the

precipitate collected by vacuum filtration, washed with 50 mL of water and dried to give 2.53 g (65% yield) of 5-(2-chloroethyl)-2-oxindole as a reddish-brown solid.

#### 5-Methoxycarbonyl-2-oxindole

5        5-Iodo-2-oxindole (17 g) was refluxed with 2 g of palladium diacetate, 18.2 g of triethylamine, 150 mL of methanol, 15 mL of dimethylsulfoxide and 2.6 g of DPPP in an atmosphere saturated with carbon monoxide. After 24 hours, the reaction was filtered to remove the catalyst and the  
10    filtrate concentrated. The concentrate was chromatographed on silica gel (30% ethyl acetate in hexane). The fractions containing product were concentrated and allowed to stand. The precipitated product was collected by vacuum filtration to give 0.8 g (7%) of the title compound as an off-white  
15    solid.

#### 4-Carboxy-2-oxindole

A solution of trimethylsilyldiazomethane in hexane (2M) was added dropwise to a solution of 2.01 g of 2-chloro-3-carboxynitrobenzene in 20 mL methanol at room temperature  
20    until no further gas evolution occurred. The excess trimethylsilyldiazo-methane was quenched with acetic acid. The reaction mixture was dried by rotary pump and the residue was further dried in a vacuum oven overnight. The product (2-chloro-3-methoxycarbonylnitrobenzene) was pure  
25    enough for the following reaction.

Dimethyl malonate (6.0 mL) was added to an ice-cold suspension of 2.1 g of sodium hydride in 15 mL of DMSO. The reaction mixture was then stirred at 100°C for 1.0 h and then cooled to room temperature. 2-Chloro-3-methoxycarbonyl-  
30    nitrobenzene (2.15 g) was added to the above mixture in one portion and the mixture was heated to 100°C for 1.5 h. The

reaction mixture was then cooled to room temperature and poured into ice water, acidified to pH 5, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated to give 3.0 g of the dimethyl 2-methoxycarbonyl-6-nitrophenylmalonate.

Dimethyl 2-methoxycarbonyl-6-nitrophenylmalonate (3.0 g) was refluxed in 50 mL of 6 N hydrochloric acid overnight. The mixture was concentrated to dryness and refluxed for 2 hours with 1.1 g of tin(II) chloride in 20 mL of ethanol. The mixture was filtered through Celite, concentrated and chromatographed on silica gel (ethyl acetate:hexane:acetic acid) to give 0.65 g (37% yield) of 4-carboxy-2-oxindole as a white solid.

15 5-Carboxy-2-oxindole

2-Oxindole (6.7 g) was added to a stirred suspension of 23 g of aluminum chloride in 30 mL of dichloroethane in an ice bath. Chloroacetyl chloride (11.3 g) was slowly added and hydrogen chloride gas was evolved. After ten minutes of stirring, the reaction was warmed at 40 to 50°C for 1.5 hours. Thin layer chromatography (ethyl acetate, silica gel) showed no remaining starting material. The mixture was cooled to room temperature and poured into ice water. The precipitate was collected by vacuum filtration, washed with water and dried under vacuum to give 10.3 g (98%) of 5-chloroacetyl-2-oxindole as an off-white solid.

A suspension of 9.3 g of 5-chloroacetyl-2-oxindole was stirred in 90 mL pyridine at 80 to 90°C for 3 hours then cooled to room temperature. The precipitate was collected by vacuum filtration and washed with 20 mL ethanol. The solid was dissolved in 90 mL 2.5N sodium hydroxide and stirred at



70 to 80°C for 3 hours. The mixture was cooled to room temperature and acidified to pH 2 with 0.5 N hydrochloric acid. The precipitate was collected by vacuum filtration and washed thoroughly with water to give crude 5-carboxy-2-oxindole as a dark brown solid. After standing overnight the filtrate yielded 2 g of 5-carboxy-2-oxindole as a yellow solid. The crude dark brown product was dissolved in hot methanol, the insoluble material removed by filtration and the filtrate concentrated to give 5.6 g of 5-carboxy-2-oxindole as a brown solid. The combined yield was 97%.

#### 5-Carboxyethyl-2-oxindole

5-Cyanoethyl-2-oxindole (4.02 g) in 10 mL of water containing 25 mL of concentrated hydrochloric acid was refluxed for 4 hours. The mixture was cooled, water added and the resulting solid collected by vacuum filtration, washed with water and dried to give 1.9 g (44% yield) of the title compound as a yellow solid.

#### 5-Iodo-4-methyl-2-oxindole

To 2 g of 4-methyl-2-oxindole in 40 mL of glacial acetic acid in an ice bath was added 3.67 g N-iodosuccinimide. The mixture was stirred for 1 hour, diluted with 100 mL 50% acetic acid in water and filtered. The resulting white solid was dried under high vacuum to give 3.27 g (88% yield) of the title compound as an off-white solid.

#### 5-Chloro-4-methyl-2-oxindole

A suspension of 3.0 g of 4-methyl-2-oxindole was stirred in 50 mL of acetonitrile at room temperature while 3.3 g of N-chlorosuccinimide was added in portions.

140

Trifluoroacetic acid (1 mL) was then added. The suspension was stirred at room temperature for 3 days during which time solid was always present. The white solid was collected by vacuum filtration, washed with a small amount of cold acetone and dried overnight in a vacuum oven at 40°C to give 2.5 g (68%) of 5-chloro-4-methyl-2-oxindole.

#### 5-Butyl-2-oxindole

Triethylsilane (2.3 g) was added to 2 g 4-butanoyl-2-oxindole in 20 mL of trifluoroacetic acid at room temperature and the solution stirred for 3 hours. The reaction was poured into ice water to give a red oil which solidified after standing. The solid was collected by vacuum filtration, washed with water and hexane and dried to give 1.7 g (91% yield) of the title compound as an off-white solid.

#### 5-Ethyl-2-oxindole

To 5-acetyl-2-oxindole (2 g) in 15 mL of trifluoroacetic acid in an ice bath was slowly added 1.8 g of triethylsilane; the reaction was then stirred at room temperature for 5 hours. One mL of triethylsilane was added and the stirring continued overnight. The reaction mixture was poured into ice water and the resulting precipitate collected by vacuum filtration, washed copiously with water and dried under vacuum to give 1.3 g (71% yield) of the title compound as a yellow solid.

#### 5-(Morpholin-4-ethyl)-2-oxindole

5-Chloroethyl-2-oxindole (2.3 g), 1.2 mL of morpholine and 1.2 mL of diisopropylethylamine were heated overnight at 100°C in 10 mL of dimethylsulfoxide. The mixture was cooled, poured into water and extracted with ethyl acetate. The

organic layer was washed with brine, dried and evaporated. The residue was chromatographed on silica gel (5% methanol in chloroform) to give 0.9 g (31%) of the title compound as a white solid.

5 5-(4-Methoxycarbonylbenzamido)-2-oxindole

A mixture of 82.0 mg 5-amino-2-oxindole and 131.0 mg 4-methoxycarbonylbenzoyl chloride in pyridine was stirred at room temperature for 3 hr and poured into ice water. The precipitate was filtered, washed with water and dried in a vacuum oven to give 138.0 mg of 5-(4-methoxycarbonylbenzamido)-2-oxindole (81% yield).

5-(4-Carboxybenzamido)-2-oxindole

5-(4-Methoxycarbonylbenzamido)-2-oxindole (0.9 g) and 0.4 g of sodium hydroxide in 25 mL of methanol were refluxed for 3 hours. The mixture was concentrated, water added, and the mixture acidified with 6N hydrochloric acid. The precipitate was collected by vacuum filtration to give 0.75 g (87%) of the title compound as a white solid.

5-Methoxy-2-oxindole

Chloral hydrate (9.6 g) was dissolved in 200 mL of water containing 83 g of sodium sulfate. The solution was warmed to 60°C, a solution of 11.4 g of hydroxylamine hydrochloride in 50 mL of water was added and the mixture was held at 60°C. In a separate flask, 6.4 g of 4-anisidine and 4.3 mL of concentrated hydrochloric acid in 80 mL of water was warmed to 80°C. The first solution was added to the second and the mixture refluxed for 2 minutes after which it was cooled slowly to room temperature and then cooled in an ice bath. The tan precipitate was collected by vacuum filtration, washed with water and dried under vacuum

to give 8.6 g ( 85% yield) of N-(2-hydroximino-acetyl)anisidine.

Concentrated sulfuric acid (45 mL) containing 5 mL of water was warmed to 60°C and 8.6 g of N-(2-hydroxi-  
5 minoacetyl) anisidine was added in one portion. The stirred mixture was heated to 93°C for 10 minutes and then allowed to cool to room temperature. The mixture was poured into 500 g of ice and extracted 3 times with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate  
10 and concentrated to give 5.1 g (65% yield) of 5-methoxyisatin as a dark red solid. 5-Methoxyisatin (5.0 g) and 30 mL of hydrazine hydrate were heated to reflux for 15 minutes. The reaction mixture was cooled to room temperature and 50 mL of water was added. The mixture was extracted 3  
15 times with 25 mL of ethyl acetate each time, the organic layers combined, dried over anhydrous sodium sulfate and concentrated to give a yellow solid. The solid was stirred in ethyl acetate and 1.1 g of insoluble material was removed by vacuum filtration and saved. This material proved to be  
20 2-hydrazinocarbonylmethyl- 4-anisidine. The filtrate was concentrated and chromatographed on silica gel eluting with ethyl acetate:hexane (1:1) to give 0.7 g of 5-methoxy-2-oxindole as a yellow solid. The 1. 1 g of 2-hydrazino- carbonylmethyl-4-anisidine was refluxed for 1  
25 hour in 20 mL of 1N sodium hydroxide. The mixture was cooled, acidified to pH 2 with concentrated hydrochloric acid and extracted 3 times with 25 mL of ethyl acetate each time. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated to give  
30 0.8 g of 5-methoxy-2-oxindole as a yellow solid. The combined yield was 1.5 g or 33%.

7-Azaoxindole

3,3-Dibromo-7-azaoxindole (2.9 g) was dissolved in a mixture of 20 mL of acetic acid and 30 mL of acetonitrile. To the solution was added 6.5 g of zinc dust. The mixture  
5 was stirred for 2 hrs at room temperature. The solid was filtered from the mixture and the solvent evaporated. The residue was slurried with ethyl acetate. The ethyl acetate solution containing insoluble solid was passed through a short column of silica gel. The collected ethyl acetate  
10 solution was evaporated and the residue dried under vacuum to give 1.8 g (yield 91%) of 7-azaoxindole acetic acid salt.

5-Dimethylaminosulfonyl-2-oxindole

A suspension of 2.3 g 5-chlorosulfonyl-2-oxindole in 10 mL 2M dimethylamine in methanol was stirred at room  
15 temperature for 4 hours at which time a white solid formed. The precipitate was collected by vacuum filtration, washed with 5 mL of 1N sodium hydroxide and 5 mL of 1N hydrochloric acid and dried under vacuum at 40°C overnight to give 1.9 g (79% yield) of 5-dimethylamino- sulfonyl-2-oxindole.

6-Phenyl-2-oxindole

Dimethyl malonate (10 mL) in 25 mL of dimethylsulfoxide was added dropwise to 3.5 g sodium hydride suspended in 25 mL dimethylsulfoxide and the mixture heated at 100°C for 10 minutes. The mixture was cooled to room temperature and 4.7  
25 g of 4-fluoro-3-nitrobiphenyl in 25 mL dimethylsulfoxide was added. The mixture was heated at 100°C for 2 hours, cooled and quenched with 300 mL of saturated ammonium chloride solution. The mixture was extracted three times with ethyl acetate and the combined organic layers washed with water  
30 and brine and evaporated to give, as a yellow oil, crude dimethyl-3-nitrobiphenyl- 4-malonate.

Crude dimethyl-3-nitrobiphenyl-4-malonate was refluxed in 30 mL of 6 N hydrochloric acid for 24 hours. The precipitate was collected by filtration, washed with water and dried to give 4.5 g of 3-nitrobiphenyl-4-acetic acid as a cream colored solid.

Iron powder (2.6 g) was added all at once to 4.5 g of 3-nitrobiphenyl-4-acetic acid in 40 mL of acetic acid. The mixture was refluxed for 2 hours, concentrated to dryness and taken up in ethyl acetate. The solids were removed by filtration and the filtrate washed twice with 1N hydrochloric acid and brine and dried over anhydrous sodium sulfate. The filtrate was concentrated to give 3.4 g (93% yield) of 6-phenyl-2-oxindole as a light brown solid.

6-(2-Methoxyphenyl)-2-oxindole

Tetrakis(triphenylphosphine)palladium (I g) was added to a mixture of 5 g 2-methoxyphenylboronic acid, 6.6 g 5-bromo-2-fluoronitrobenzene and 30 mL of 2 M sodium carbonate solution in 50 mL of toluene and 50 mL of ethanol. The mixture was refluxed for 2 hours, concentrated, and the residue extracted twice with ethyl acetate. The ethyl acetate layer was washed with water and brine, then dried, and concentrated to give a dark green oil which solidified on standing, crude 4-fluoro-2'-methoxy-3-nitrobiphenyl.

Dimethyl malonate (14 mL) was added dropwise to 2.9 g of sodium hydride suspended in 50 mL of dimethylsulfoxide. The mixture was heated at 100°C for 15 minutes and cooled to room temperature. Crude 4-fluoro-2'-methoxy-3-nitrobiphenyl in 60 mL of dimethylsulfoxide was added and the mixture was heated at 100°C for 2 hours. The reaction mixture was cooled and quenched with 300 mL of saturated sodium chloride solution and extracted twice with ethyl acetate. The

extracts were combined, washed with saturated ammonium chloride, water and brine, dried over anhydrous sodium sulfate and concentrated to give crude dimethyl 2'-methoxy-3-nitrobiphenyl-4-malonate as a yellow oil.

5        Crude dimethyl 2'-methoxy-3-nitrobiphenyl-4-malonate was heated at 100°C in 50 mL of 6 N hydrochloric acid for 24 hours and cooled. The precipitate was collected by filtration, washed with water and hexane, and dried to give 9.8 of 2'-methoxy-2-nitrobiphenyl-4acetic acid as a light  
10    tan solid.

      Iron powder (5 g) was added in one portion to 9.8 g of 2'-methoxy-3-nitrobiphenyl-4-acetic acid in 50 mL of glacial acetic acid was heated to 100°C for 3 hours. The reaction mixture was concentrated to dryness, sonicated in ethyl  
15    acetate and filtered to remove the insolubles. The filtrate was washed twice with 1N hydrochloric acid, water and then brine, dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on silica gel in ethyl acetate:hexane (1:2) to give 5.4 g of  
20    6-(2-methoxyphenyl)-2-oxindole as a rose colored solid.

6-(3-Methoxyphenyl)-2-oxindole

      Tetrakis(triphenylphosphine)palladium (0.8 g) was added to a mixture of 5 g 3-methoxyphenylboronic acid, 5 g 5-bromo-2-fluoro-nitrobenzene and 11 mL of 2 M sodium  
25    carbonate solution in 100 mL of toluene. The mixture was refluxed for 2 hours, diluted with water and extracted with ethyl acetate. The ethyl acetate was washed with saturated sodium bicarbonate and brine and then dried and concentrated to give an oily solid. The solid was chromatographed on  
30    silica gel (ethyl acetate:hexane (1:6)) to give 4.3 g (77% yield) of 4-fluoro-3'-methoxy-3-nitrobiphenyl.

Dimethyl malonate (9.7 mL) was added dropwise to 2.0 g sodium hydride suspended in 50 mL dimethylsulfoxide. The mixture was heated to 100°C for 35 minutes and cooled to room temperature. 4-Fluoro-2'-methoxy-3-nitrobiphenyl (4.2 g) in 50 mL dimethylsulfoxide was added and the mixture was heated at 100°C for 1 hour. The reaction mixture was cooled and quenched with 300 mL of saturated ammonium chloride solution and extracted twice with ethyl acetate. The extracts were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated to give crude dimethyl 3'-methoxy-3-nitrobiphenyl-4-malonate as a pale yellow solid.

Crude dimethyl 3'-methoxy-3-nitro-biphenyl-4-malonate was heated at 110°C in 45 mL 6N hydrochloric acid for 4 days and then cooled. The precipitate was collected by filtration, washed with water and hexane, and dried to give 5.3 g of 3'-methoxy-2-nitrobiphenyl-4-acetic acid as a light tan solid.

3'-Methoxy-3-nitrobiphenyl-4-acetic acid (5.2 g) was dissolved in methanol and hydrogenated over 0.8 g of 10% palladium on carbon for 3 hours at room temperature. The catalyst was removed by filtration, washed with methanol and the filtrates combined and concentrated to give a brown solid. The solid was chromatographed on silica gel in ethyl acetate:hexane:acetic acid (33:66:1) to give 3.0 g of 6-(3-methoxyphenyl)-2-oxindole as a pink solid.

#### 6-(4-Methoxyphenyl)-2-oxindole

Tetrakis(triphenylphosphine)palladium (I g) was added to a mixture of 5 g of 4-methoxyphenylboronic acid, 6.6 g of 5-bromo-2-fluoronitrobenzene and 30 mL of 2 M sodium carbonate solution in 50 mL of toluene and 50 mL of ethanol.



The mixture was refluxed for 2 hours, concentrated, and the residue extracted twice with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried, and concentrated to give a brown oily solid. The solid was  
5 chromatographed on silica gel (5% ethyl acetate in hexane) to give crude 4-fluoro-4'-methoxy-3-nitrobiphenyl as a pale yellow solid.

Dimethyl malonate (10 mL) was added dropwise to 2.0 g of sodium hydride suspended in 60 mL of dimethylsulfoxide.  
10 The mixture was heated to 100°C for 10 minutes and cooled to room temperature. Crude 4-fluoro-2'-methoxy-3-nitrobiphenyl (5.2 g) in 50 mL dimethylsulfoxide was added and the mixture was heated at 100°C for 2 hours. The reaction mixture was cooled and quenched with 300 mL of saturated sodium chloride  
15 solution and extracted three times with ethyl acetate. The extracts were combined, washed with saturated ammonium chloride, water and brine, dried over anhydrous sodium sulfate and concentrated to give crude dimethyl 4'-methoxy-3-nitrobiphenyl-4malonate as a yellow oil.

Crude dimethyl 4'-methoxy-3-nitrobiphenyl-4-malonate  
20 was heated at 100°C in 60 mL of 6N hydrochloric acid for 15 hours and cooled. The precipitate was collected by filtration, washed with water and hexane, and dried to give 7.2 g of crude 4'-methoxy-3nitrobiphenyl-4-acetic acid as a  
25 light tan solid.

Iron powder (3.6 g) was added in one portion to 7.2 g of 4'-methoxy-3-nitrobiphenyl-4-acetic acid in 50 mL of glacial acetic acid and heated at 100°C overnight. The reaction mixture was concentrated to dryness, sonicated in  
30 ethyl acetate and filtered to remove the insolubles. The filtrate was washed twice with 1N hydrochloric acid and brine, dried over anhydrous sodium sulfate and concentrated

to give 2.7 g of 6-(4-methoxyphenyl)-2-oxindole as a rose colored solid.

6-(3-Ethoxyphenyl)-2-oxindole

Tetrakis(triphenylphosphine)palladium (0.8 g) was added  
5 to a mixture of 4.2 g of 3-ethoxyphenylboronic acid, 5.0 g  
of 5-bromo-2-fluoronitrobenzene and 22 mL of 2 M sodium  
carbonate solution in 50 mL of toluene and 50 mL of ethanol.  
The mixture was refluxed for 2 hours, concentrated, water  
was added and the mixture was extracted twice with ethyl  
10 acetate. The ethyl acetate layer was washed with water and  
brine, then dried, and concentrated. The residue was  
chromatographed on silica gel (5% ethyl acetate in hexane)  
to give 5.3 g (90% yield) of crude 4-fluoro-3'-ethoxy-3-  
nitrobiphenyl as a yellow oil.

15 Dimethyl malonate (11.4 mL) was added dropwise to 4.0 g  
sodium hydride suspended in 20 mL dimethylsulfoxide. The  
mixture was heated to 100°C for 10 minutes and then cooled  
to room temperature. Crude 4-fluoro-3'-ethoxy-3-nitro-  
biphenyl (5.3 g) in 25 mL of dimethylsulfoxide was added and  
20 the mixture was heated at 100°C for 2 hours. The reaction  
mixture was cooled and quenched with 300 mL of saturated  
ammonium chloride solution and extracted three times with  
ethyl acetate. The extracts were combined, washed with water  
and brine and then dried over anhydrous sodium sulfate and  
25 concentrated to give crude dimethyl 3'-ethoxy-3-nitro-  
biphenyl-4-malonate as a yellow oil.

Crude dimethyl 3'-ethoxy-3-nitrobiphenyl-4-malonate was  
heated at 100°C in 60 mL of 6N hydrochloric acid for 4 days  
and then cooled. The precipitate was collected by  
30 filtration, washed with water and hexane, and dried to give

4.7 g of crude 3'-ethoxy-3-nitrobiphenyl-4-acetic acid as a light tan solid.

Iron powder (2.4 g) was added in one portion to 4.6 g of 3'-ethoxy-3-nitrobiphenyl-4-acetic acid in 40 mL of glacial acetic acid and refluxed for 2 hours. The reaction mixture was concentrated to dryness, treated repeatedly with ethyl acetate and filtered to remove the insolubles. The filtrate was washed twice with 1N hydrochloric acid and brine and then dried over anhydrous sodium sulfate and concentrated to give 3.5 g (91% yield) of 6-(3-ethoxyphenyl)-2-oxindole as a light brown solid.

#### 6-Bromo-2-oxindole

Dimethyl malonate (13 mL) was added dropwise to 2.7 g sodium hydride suspended in 20 mL dimethylsulfoxide. The mixture was heated to 100°C for 10 minutes and then cooled to room temperature. 5-Bromo-2-fluoronitrobenzene (5.0 g) in 25 mL of dimethylsulfoxide was added and the mixture was heated at 100°C for 2 hours. The reaction mixture was cooled and quenched with 300 mL of saturated ammonium chloride solution and extracted three times with ethyl acetate. The extracts were combined, washed with saturated ammonium chloride, water and brine, dried over anhydrous sodium sulfate and concentrated to give crude dimethyl 4-bromo-2-nitrophenylmalonate as a pale yellow oil.

Crude dimethyl 4-bromo-2-nitrophenylmalonate was heated at 110°C in 40 mL of 6N hydrochloric acid for 24 hours and then cooled. The precipitate was collected by filtration, washed with water and dried to give 5.3 g (89% yield) of 4-bromo-2-nitro-phenylacetic acid as an off white solid.

4-Bromo-2-nitrophenylacetic acid (0.26 g), 0.26 g zinc powder and 3 mL 50% sulfuric acid in 5 mL of ethanol were

150

heated at 100°C overnight. The reaction mixture was filtered, diluted with a little acetic acid, concentrated to remove ethanol, diluted with water and extracted twice with ethyl acetate. The combined extracts were washed with brine,  
5 dried over anhydrous sodium sulfate and concentrated to give 0.19 g (90% yield) of 6-bromo-2-oxindole as a yellow solid.

#### 5-Acetyl-2-oxindole

2-Oxindole (3 g) was suspended in 1,2-dichloroethane and 3.2 mL acetyl chloride were slowly added. The resulting  
10 suspension was heated to 50°C for 5 hours, cooled, and poured into water. The resulting precipitate was collected by vacuum filtration, washed copiously with water and dried under vacuum to give 2.9 g (73% yield) of the title compound as a brown solid.

#### 15 5-Butanoyl-2-oxindole

To 15 g aluminum chloride suspended in 30 mL 1,2-dichloro- ethane in an ice bath was added 7.5 g of 2-oxindole and then 12 g of butanoyl chloride. The resulting suspension was heated to 50°C overnight. The mixture was  
20 poured into ice water and extracted 3 times with ethyl acetate. The combined ethyl acetate layers were washed with brine, dried over sodium sulfate, and concentrated to dryness to give a brown solid. The solid was chromatographed on silica gel (50% ethyl acetate in hexane) to give 3 g  
25 (25%) of the title compound as a yellow solid.

#### 5-Cyanoethyl-2-oxindole

Potassium cyanide (2.0 g) was added to 15 mL of dimethyl-sulfoxide and heated to 90°C. 5-Chloroethyl-2-oxindole (3.0 g) dissolved in 5 mL dimethyl sulfoxide was  
30 added slowly with stirring, and the reaction heated to 150°C

for 2 hours. The mixture was cooled, poured into ice water and the precipitate collected by vacuum filtration, washed with water, dried and then chromatographed on silica gel (5% methanol in chloroform) to give 1.2 g (42% yield) of the  
5 title compound.

6-(Morpholin-4-yl)-2-oxindole

6-Amino-2-oxindole (2.2 g), 4.0 g 2, 2'-dibromoethyl ether and 7.9 g sodium carbonate were refluxed in 20 ml ethanol overnight, concentrated and diluted with 50 ml of  
10 water. The mixture was extracted three times with 50 ml of ethyl acetate and the organic extracts combined, washed with 20 ml of brine, dried over anhydrous sodium sulfate and concentrated to dryness. The solid was chromatographed on a column of silica gel (ethyl acetate:hexane (1:1) containing  
15 0.7% acetic acid) to give 1.2 g (37% yield) of the title compound as a beige solid.

6-(3-Trifluoroacetylphenyl)-2-oxindole

3-Aminophenylboronic acid (3.9 g), 5 g 5-bromo-2-fluoro- nitrobenzene, 0.8 g tetrakis (triphenylphosphine)  
20 palladium and 23 mL of 2 M sodium bicarbonate solution in 50 mL of toluene were refluxed under nitrogen for 2.5 hours. The reaction mixture was poured into 200 mL of ice water and the mixture extracted three times with 50 mL of ethyl acetate. The combined organic layers were washed with 50 mL  
25 of water and 20 mL of brine, dried over anhydrous sodium sulfate and concentrated to give 9.7 g (92% yield) of 2-fluoro-5-(3-aminophenyl)nitrobenzene as a dark brown oil.

Trifluoroacetic anhydride (5.4 mL) was slowly added to a stirred solution of 9.7 g 2-fluoro-5-(3-aminophenyl)-  
30 nitrobenzene and 5.3 mL of triethylamine in 50 mL of dichloromethane at 0°C and the mixture was stirred for an

additional 20 minutes. The mixture was concentrated and the residue chromatographed on a column of silica gel (10% ethyl acetate in hexane) to give 8.6 g (65% yield) of 2-fluoro-5-(3-trifluoroacetamidophenyl)nitrobenzene as a pale orange oil which solidified on standing.

Dimethyl malonate (9.6 mL) was added dropwise to a stirred suspension of 3.2 g of 60% sodium hydride in mineral oil in 40 mL anhydrous dimethylsulfoxide under nitrogen. The mixture was stirred for 10 minutes and 2-fluoro-5-(3-trifluoroacetamidophenyl)nitrobenzene in 20 mL dimethylsulfoxide was added. The resulting dark red mixture was heated to 100°C for 2 hours. The reaction was quenched by pouring into 100 mL of saturated ammonium chloride solution and extracted twice with 50 mL of ethyl acetate. The organic phase was washed with 50 mL each of saturated ammonium chloride solution, water, and brine, dried over anhydrous sodium sulfate and concentrated to a yellow oil. The oil was chromatographed on a column of silica gel (ethyl acetate:hexane (1:4)) to give 4.4 g (50% yield) of dimethyl 2-[2-nitro-4-(3-trifluoroacetamidophenyl)phenyl]-malonate as a pale yellow solid.

Dimethyl 2-[2-nitro-4-(3-trifluoroacetamidophenyl)phenyl]-malonate (4.4 g) was refluxed overnight in 50 mL 6N hydrochloric acid. The reaction mixture was cooled to room temperature and the solids were collected by vacuum filtration, washed with water, and dried under vacuum to give 2.7 g (73% yield) of 2-[2-nitro-4-(3-trifluoroacetamidophenyl)phenyl]acetic acid.

2-[2-Nitro-4-(3-trifluoroacetamidophenyl)phenyl]acetic acid (100 mg) and 50 mg iron powder in 3 mL acetic acid was heated at 100°C for 2 hours. The reaction mixture was concentrated and the residue sonicated in 5 mL ethyl

acetate. The insoluble solids were removed by vacuum filtration and the filtrate washed with 1N hydrochloric acid, water and brine, dried over anhydrous sodium sulfate and concentrated to give 10 mg (14% yield) of the title compound as a rose-colored solid.

A list of oxindoles which can be prepared by the above procedures as well as by other procedures known in the chemical arts and which are useful for preparing compounds of this invention are shown in Table 5. The oxindoles in Table 5 are shown by way of example only and are not to be construed as in any way limiting the scope of this invention.

#### C. Aldehydes

Aldehydes useful for the synthesis of compounds of this invention can be prepared by numerous synthetic procedures well known to those skilled in the art. For example, and not limitation, the procedures described in the following publications, which are incorporated by reference as if fully set forth herein, can be employed to give some of the aldehydes of this invention:

J. Med. Chem., 1993, 36(23), 3674-3685;

Chem. Commun., 1966, 393.

Chem. Heterocycl. Compd. (EN), 1974, 10, 50-52; and

J. Chem. Soc. Perkin Trans., 1:EN, 1974, 1237-1243.

Table 6 lists additional aldehydes which can be used to make compounds of this invention. The oxindoles in Table 6 are shown by way of example only and are not to be construed as in any way limiting the scope of this invention.

#### 5. BIOLOGICAL EVALUATION

It will be appreciated that, in any given series of compounds, a spectrum of biological activities will be

obtained. In its preferred embodiments, this invention relates to novel 2-indolinones demonstrating the ability to modulate RTK, CTK, and STK activity. The following assays are employed to select those compounds demonstrating the optimal degree of the desired activity.

A. Description of the Tables.

Table 1 is a list of some compounds of this invention. The compounds in the list are shown by way of example only and in no way are to be considered limiting on the scope of this invention.

Table 2 is a list of some compounds of this invention. The compounds in the list are shown by way of example only and in no way are to be considered limiting on the scope of this invention.

Table 3 is a list of some compounds of this invention. The compounds in the list are shown by way of example only and in no way are to be considered limiting on the scope of this invention.

Table 4 is a list of some compounds of this invention. The compounds in the list are shown by way of example only and in no way are to be considered limiting on the scope of this invention.

Table 5 is a list of oxindoles which may be used to prepare compounds of this invention. The oxindoles in the list are shown by way of example only and in no way are to be considered limiting on the scope of this invention.

Table 6 is a list of aldehydes which may be used to prepare compounds of this invention. The oxindoles in the list are shown by way of example only and in no way are to be considered limiting on the scope of this invention.



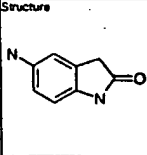
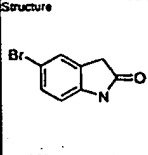
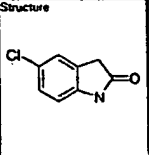
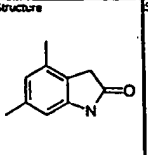
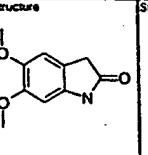
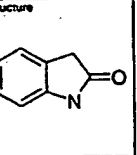
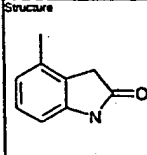
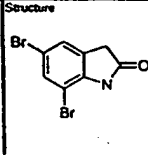
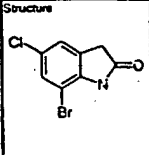
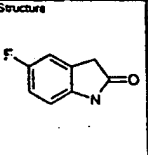
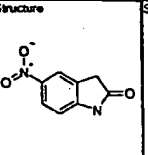
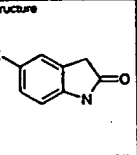
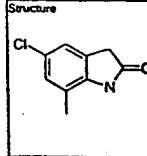
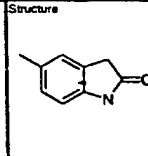
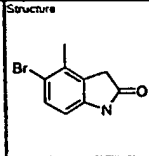
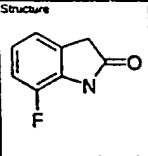
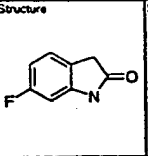
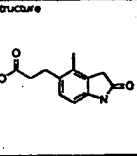
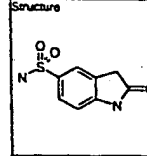
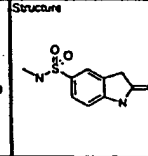
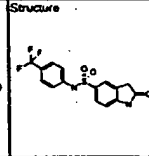
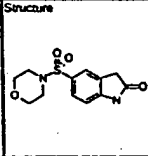
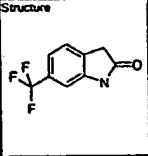
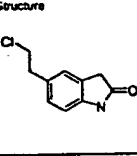
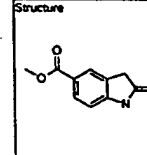
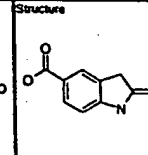
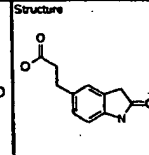
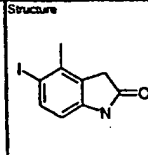
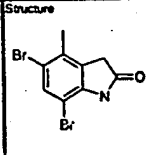
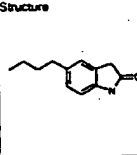
Table 7 shows the results of biological assays using representative, but by no means limiting, examples of compounds of this invention.  $IC_{50}$  refers to that amount of the tested compound needed to effect a 50% change in the activity of the PTK in the test indicated with respect to a control in which no compound of this invention is present. With regard to the tests in the table, the 50% change being evaluated is a 50% inhibition of PTK activity over that of the control. The assay procedures employed are described in detail below.

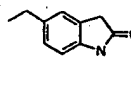
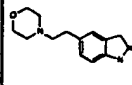
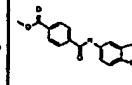
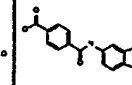
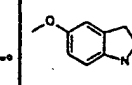
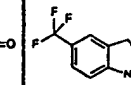
Table 8 shows the results of additional biological assays using representative, but by no means limiting, examples of compounds of this invention. Once again,  $IC_{50}$  refers to that amount of the tested compound needed to effect a 50% change in the activity of the PTK in the test indicated with respect to a control in which no compound of this invention is present. With regard to the tests in the table, the 50% change being evaluated is a 50% inhibition of PTK activity over that of the control. As above, the assay procedures employed are described in detail below.

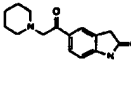
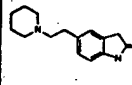
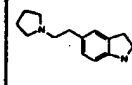
Table 9 likewise shows the results of additional biological assays using representative, but by no means limiting, examples of compounds of this invention. Once again,  $IC_{50}$  refers to that amount of the tested compound needed to effect a 50% change in the activity of the PTK in the test indicated with respect to a control in which no compound of this invention is present. With regard to the tests in the table, the 50% change being evaluated is a 50% inhibition of PTK activity over that of the control. As above, the assay procedures employed are described in detail below.

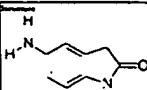
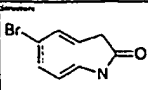
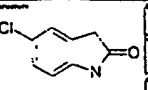
Table 10 also shows the results of additional biological assays using representative, but by no means limiting, examples of compounds of this invention. In this case, the compounds tested are those listed in Table 3. In 5 this series of tests, the percent inhibition of the PK indicated compared to a non-treated standard is shown. As previously noted, the assay procedures employed are described in detail below.

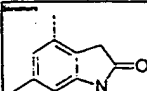
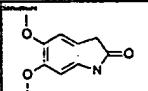
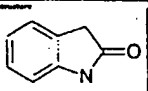
TABLE 5

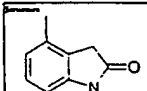
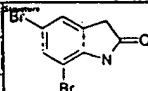
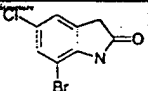
					
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Name OXINDOLE-013	Name OXINDOLE-014	Name OXINDOLE-015	Name OXINDOLE-016	Name OXINDOLE-019	Name OXINDOLE-028
					
Name OXINDOLE-036	Name OXINDOLE-037	Name OXINDOLE-038	Name OXINDOLE-039	Name OXINDOLE-040	Name OXINDOLE-041
					
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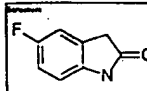
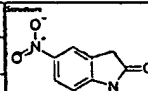
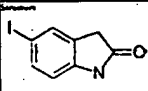
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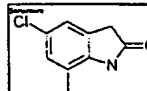
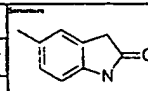
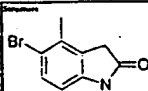
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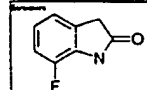
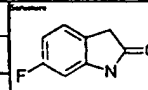
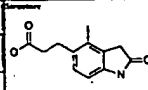
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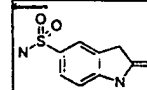
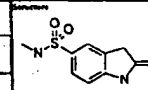
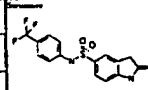
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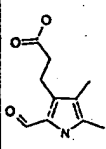
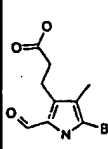
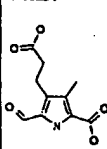
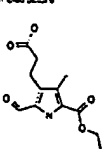
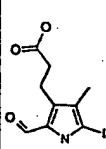
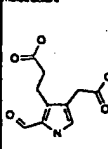
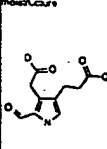
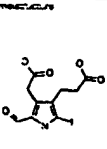
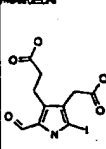
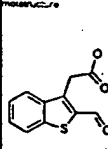
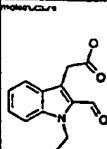
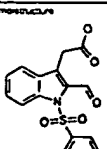
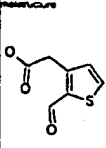
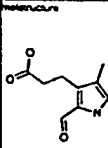
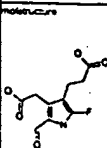
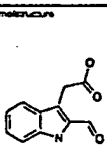
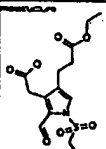
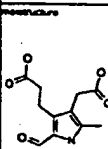
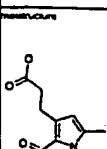
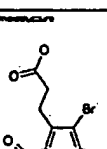
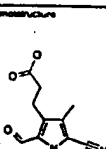
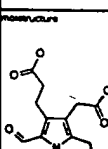
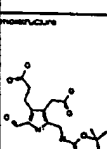
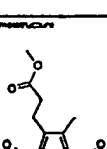
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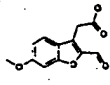
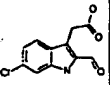
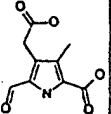
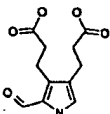
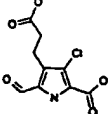
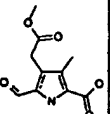
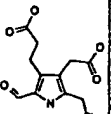
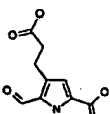
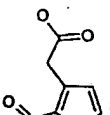
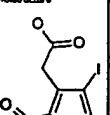
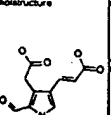
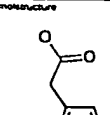
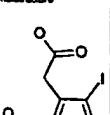
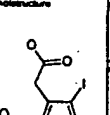
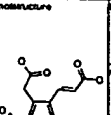
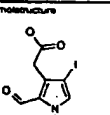
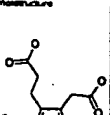
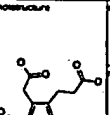
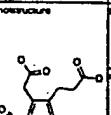
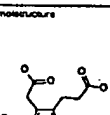
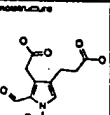
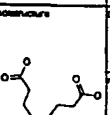
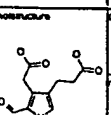
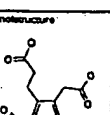
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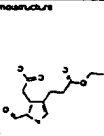
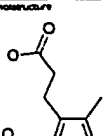
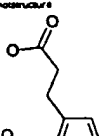
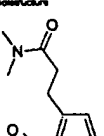
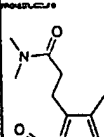
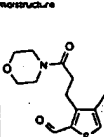
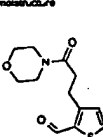
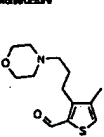
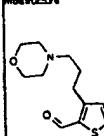
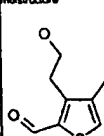
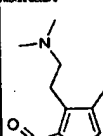
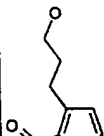
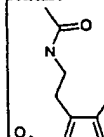
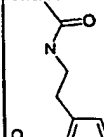
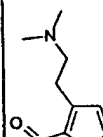
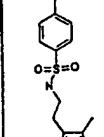
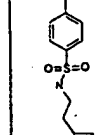
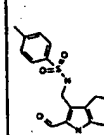
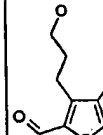
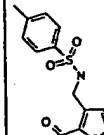
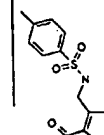
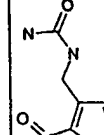
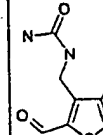
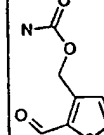
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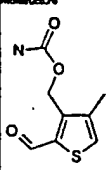
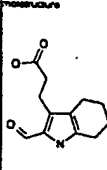
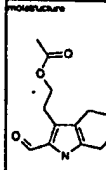
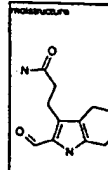
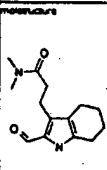
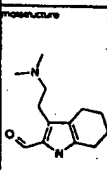
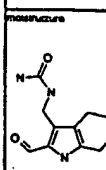
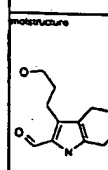
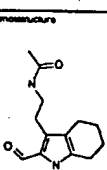
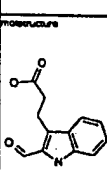
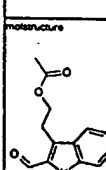
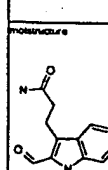
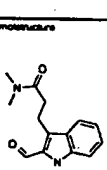
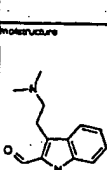
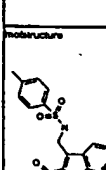
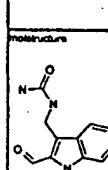
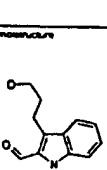
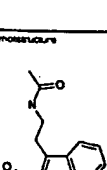
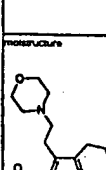
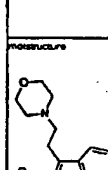
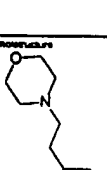
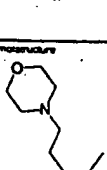
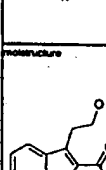
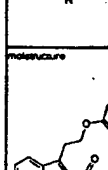
TABLE 6

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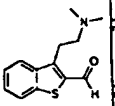
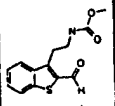
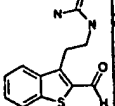
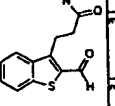
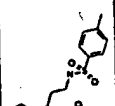
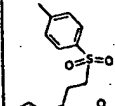
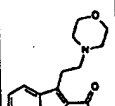
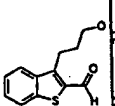

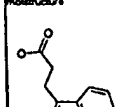
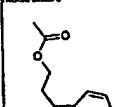
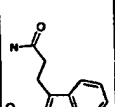
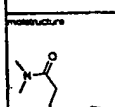
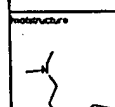
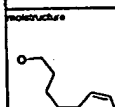
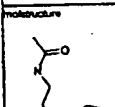
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 Structure	CORP. ID 105	 Structure	CORP. ID 106	 Structure	CORP. ID 107	 Structure	CORP. ID 108
 Structure	CORP. ID 109	 Structure	CORP. ID 110	 Structure	CORP. ID 111	 Structure	CORP. ID 112

Table 7

NAME	FLK-1R IC50 ( $\mu$ M)	PDGFR IC50 ( $\mu$ M)	EGFR IC50 ( $\mu$ M)	HUV-EC-C VEGF ( $\mu$ M)	(ATCC) aFGF ( $\mu$ M)	SRC ( $\mu$ M)	LCK ( $\mu$ M)	FAK ( $\mu$ M)
3-(4, 5, 6, 7-tetrahydroindole-2-methylidenyl)-5-[N,N-dimethylaminosulfonyl]-2-indolinone	>100	>100	>100.0			0.1	0.5	>10
3-(4, 5, 6, 7-tetrahydroindole-2-methylidenyl)-5-[aminosulfonyl]-2-indolinone	>100.0	1	>100.0	0.65 1.07	2.4 3.3	0.8	0.7	>10

Table 8

5

NAME	PDGFR	FLK-1R IC50 ( $\mu$ M)	EGFR IC50 ( $\mu$ M)	HER2 Kinase IC50 ( $\mu$ M)	IGF-1R IC50 ( $\mu$ M)
3-[2-ethoxycarbonyl-3-(2-ethoxycarbonylethyl)-4-(ethoxycarbonylmethyl)pyrrol-5-methylidenyl]-2-indolinone	>10	>10	>10	>10	>10
3-(2-carboxy-4-ethyl-3-methylpyrrol-5-methylidenyl)-2-indolinone	>100	36.2	>100	>100	>100
3-(2-chloro-4-methoxycarbonyl-3-methoxycarbonylmethylpyrrol-5-methylidenyl)-2-indolinone	>50	>50	>50	>50	>50
3-(4-acetyl-2-ethoxycarbonyl-3-methylpyrrol-5-methylidenyl)-2-indolinone	>10	>10	>10	0	>10
3-(4-ethoxycarbonyl-3-methylpyrrol-2-methylidenyl)-2-indolinone	>100	0.2	>100	>100	>100
3-[3-(2-carboxyethyl)-4-methylpyrrol-2-methylidenyl]-2-indolinone	>100	0.4	>100	>100	>100
3-(2-acetyl-3,4-dimethylpyrrol-5-methylidenyl)-2-indolinone	>100	23.8	>100	>100	>100
3-[4-(2-methoxycarbonylethyl)-3-methylpyrrol-2-methylidenyl]-2-indolinone	>53.7	1.1	>100	>100	>100

167

NAME	PDGFR	FLK-1R IC50 (uM)	EGFR IC50 (uM)	HER2 Kinase IC50 (uM)	IGF-1R IC50 (uM)
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-2-indolinone	>100	0.07	>100	>100	>100
3-[4-(2-methoxycarbonylethyl)-3-methylpyrrol-2-methylidenyl]-5,6-dimethoxy-2-indolinone	22.3	36	>50	>50	>50
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-5-(4-methoxycarbonylbenzamido)-2-indolinone		>10	>10	>10	>10
3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-5-bromo-2-indolinone	15	4.2	>25	>25	>100

TABLE 9

Name	CDK2-IC50, $\mu$ M
3-(2-imidazoylemethylydenyl)-5-chloro-2-indolinone	19.1
3-(2-imidazoylemethylydenyl)-5-amino-2-indolinone	11.9
3-(2-imidazoylemethylydenyl)-2-indolinone	<0.78
3-(4-imidazoylemethylydenyl)-5-methyl-2-indolinone	1.1
3-(4-imidazoylemethylydenyl)-5-nitro-2-indolinone	<0.78
3-(4-imidazoylemethylydenyl)-5-chloro-2-indolinone	<0.78
3-(4-imidazoylemethylydenyl)-5-chloro-7-indolinone	9.3
3-(4-imidazoylemethylydenyl)-5-fluoro-2-indolinone	7.7
3-(4-imidazoylemethylydenyl)-5-amino-2-indolinone	<0.78
3-(4-imidazoylemethylydenyl)-4,6-dimethyl-2-indolinone	<0.78
3-(4-imidazoylemethylydenyl)-5,6-dimethoxy-2-indolinone	2.4

TABLE 10

Barcode/ Plate Row- Plate Column	Fik Kinase %Inhibition	Biochem EGFR %Inhibition	PDGF Kinase %Inhibition	Met Kinase %Inhibition
10717/H02	4.0	3.5		44.5
10717/H03	8.6	25.7		18.3
10717/H04	0.4	6.8		14.0
10717/H05	5.0	-2.0		16.3
10717/H06	12.5	-16.8		30.5
10717/H07	1.1	91.2		9.1
10717/H08	-8.4	33.4		23.0
10717/H09	-17.5	5.4		8.8
10717/H10	-5.0	0.5		52.3
10717/H11	-0.4	55.6		58.2
10718/H02	-1.4	-22.5		31.5
10718/H03	-5.0	33.2		90.8
10718/H04	-5.7	13.7		84.3
10718/H05	1.0	0.2		13.5
10718/H06	18.2	-5.1		32.2
10718/H07	-3.0	-12.0		52.7
10718/H08	-0.5	-2.5		14.4
10718/H09	-5.0	34.2		73.6
10718/H10	1.4	-5.7		19.9
10718/H11	13.0	4.4		44.9
10719/H02	22.0	43.9		36.9
10719/H03	-40.4	25.1		67.0
10719/H04	3.4	-0.5		0.7
10719/H05	18.5	7.9		20.9
10719/H06	17.8	-28.0		1.3
10719/H07	2.4	-2.8		22.9
10719/H08	11.6	2.9		20.0
10719/H09	2.5	-33.5		5.8
10719/H10	-0.7	14.6		-5.7
10719/H11	12.3	-12.0		50.5
10720/H02	9.7	17.0		64.1
10720/H03	1.8	-13.9		40.0
10720/H04	-5.8	-49.6		21.3
10720/H05	-12.3	-29.0		51.0
10720/H06	22.3	-52.4		24.4
10720/H07	-2.9	-49.8		10.8
10720/H08	-23.7	-55.8		40.0
10720/H09	-4.5	-66.8		49.0
10720/H10	-22.8	-62.8		48.2
10720/H11	-8.8	-19.3		28.0
10721/H02	5.5	20.1		39.7
10721/H03	7.8	29.2		21.3
10721/H04	0.7	-8.5		72.9
10721/H05	-8.4	-12.4		33.6

10721/H06	-7.9	43.3		90.3
10721/H07	-7.0	-20.5		10.4
10721/H08	-6.8	-6.8		42.5
10721/H09	7.0	-10.4		36.7
10721/H10	10.2	-3.9		46.9
10721/H11	-6.0	-21.3		46.0
10722/H02	4.2	24.8	19.2	37.8
10722/H03	2.1	27.8	26.6	100.5
10722/H04	3.8	8.6	-26.1	62.2
10722/H05	4.3	1.1	0.9	83.2
10722/H06	18.9	-2.0	18.6	70.3
10722/H07	2.3	-24.8	-16.9	51.0
10722/H08	-20.3	-5.7	-15.2	72.6
10722/H09	3.3	-7.4	17.5	67.6
10722/H10	-14.1	11.2	7.2	30.3
10722/H11	-3.3	-16.3	15.7	66.1
10723/H02	9.0	72.8	20.7	100.8
10723/H03	6.1	6.3	-30.6	69.2
10723/H04	-20.2	7.1	53.3	95.6
10723/H05	-2.5	-17.3	-12.6	64.2
10723/H06	10.6	-11.8	-17.4	44.9
10723/H07	5.0	-11.3	-20.9	44.9
10723/H08	-4.2	69.9	4.1	86.2
10723/H09	-0.4	-2.6	15.9	62.1
10723/H10	-13.4	-38.1	-22.3	46.4
10723/H11	-5.1	-20.7	29.7	76.2
10724/H02	11.5	17.6	2.2	51.9
10724/H03	1.8	0.3	-7.6	26.1
10724/H04	-3.0	14.0	-13.1	69.3
10724/H05	-0.4	-1.3	-19.4	68.6
10724/H06	-5.1	-8.2	-20.8	32.8
10724/H07	1.1	-19.3	-39.6	8.6
10724/H08	13.1	-19.7	-9.0	65.8
10724/H09	1.3	-33.5	-13.1	4.2
10724/H10	5.8	-25.5	-2.7	72.2
10724/H11	8.6	-12.8	-31.2	9.8
10725/H02	-7.6	-23.5	-19.9	15.8
10725/H03	-5.8	-16.5	-12.8	58.3
10725/H04	-5.1	17.2	-4.1	47.1
10725/H05	21.6	-30.2	14.6	20.8
10725/H06	16.1	0.3	6.9	33.0
10725/H07	8.6	-13.3	2.6	14.2
10725/H08	17.2	-3.7	13.6	5.7
10725/H09	-6.1	-28.4	9.3	41.6
10725/H10	7.8	9.1	12.2	21.8
10725/H11	-40.8	0.5	16.5	17.8
10726/H02	-8.5	-11.2	-8.3	66.6



10726/H03	0.4	14.0	-17.8	44.8
10726/H04	2.5	75.5	13.2	77.6
10726/H05	-6.1	2.2	-38.0	80.2
10726/H06	17.5	-9.2	-20.9	35.1
10726/H07	-9.5	31.2	-30.4	80.9
10726/H08	-15.0	-16.6	15.1	71.2
10726/H09	1.5	-0.1	15.1	68.1
10726/H10	11.0	12.0	6.9	45.7
10726/H11	12.9	1.5	-0.1	40.8
10727/H02	-1.2	-37.1	-33.6	55.5
10727/H03	4.3	4.5	-20.5	49.2
10727/H04	1.8	19.2	13.7	81.7
10727/H05	5.5	0.4	-28.5	20.6
10727/H06	-4.4	-35.8	-40.8	5.2
10727/H07	-9.7	-17.3	-37.2	26.8
10727/H08	2.9	-8.0	-27.0	12.3
10727/H09	-1.4	-6.1	-11.7	31.1
10727/H10	-8.3	83.6	10.1	89.7
10727/H11	3.7	-3.5	2.8	17.9
10728/H02	-13.3	-36.6	-9.3	25.8
10728/H03	-2.1	3.5	-10.6	15.6
10728/H04	-4.3	-0.6	-5.7	32.9
10728/H05	1.1	-13.5	-10.6	41.2
10728/H06	7.9	-22.8	-25.7	28.5
10728/H07	1.5	-25.8	-1.7	45.8
10728/H08	-4.4	-3.4	-5.3	33.9
10728/H09	0.7	-6.1	-6.2	30.5
10728/H10	-3.8	-22.4	4.5	65.2
10728/H11	3.3	-25.6	-16.8	8.0
10729/H02	14.3	-10.7	2.3	25.5
10729/H03	18.3	30.3	-0.7	2.8
10729/H04	1.1	-4.4	-5.6	25.1
10729/H05	22.4	-4.4	-27.6	27.9
10729/H06	11.0	-10.3	-12.1	28.4
10729/H07	9.9	30.0	-43.1	81.0
10729/H08	8.2	8.7	-1.5	44.0
10729/H09	-2.7	8.0	0.1	45.1
10729/H10	5.3	2.1	-1.5	12.8
10729/H11	8.9	0.8	5.0	36.1
10730/H02	21.2	12.6	1.0	32.0
10730/H03	11.5	-3.4	-11.7	28.3
10730/H04	12.1	-29.5	-1.2	37.1
10730/H05	11.7	-20.1	22.1	30.7
10730/H06	15.7	-13.5	-9.9	13.4
10730/H07	19.0	-3.2	0.6	38.7
10730/H08	9.2	-15.8	6.3	57.8
10730/H09	16.6	11.1	7.2	41.1

10730/H10	18.3	1.7	23.0	24.9
10730/H11	13.9	26.4	9.4	32.6
10731/H02	19.7	-9.5	-18.7	16.4
10731/H03	20.0	-1.5	1.8	23.3
10731/H04	16.4	-1.7	-15.8	41.0
10731/H05	23.6	-3.6	-1.6	32.2
10731/H06	28.7	-7.8	-5.4	17.2
10731/H07	74.5	-1.7	36.5	1.8
10731/H08	31.4	-0.5	-10.1	10.9
10731/H09	15.8	-2.7	-5.4	12.8
10731/H10	25.9	3.5	40.3	28.4
10731/H11	27.8	-3.1	8.9	6.9
10732/H02	9.1	13.0	6.8	56.8
10732/H03	8.4	1.4	-1.8	24.1
10732/H04	4.9	-0.7	14.4	57.6
10732/H05	12.8	-2.9	-25.6	13.3
10732/H06	22.6	-6.9	-18.0	31.1
10732/H07	9.7	-15.3	-22.0	26.7
10732/H08	12.6	-14.0	7.8	38.7
10732/H09	5.4	-7.4	-14.4	49.8
10732/H10	3.3	-21.3	-21.0	28.0
10732/H11	6.4	-15.1	-16.0	46.7
10733/H02	-2.0	3.2	-5.6	38.9
10733/H03	31.2	-16.5	16.8	0.6
10733/H04	-8.5	-24.0	-14.5	11.9
10733/H05	17.7	15.9	-15.3	5.6
10733/H06	30.0	-10.5	-12.9	18.4
10733/H07	7.6	-6.2	-19.0	-1.3
10733/H08	4.8	0.3	-15.3	41.6
10733/H09	44.8	-3.1	5.0	51.9
10733/H10	12.6	-3.1	10.7	26.5
10733/H11	29.1	7.0	-4.8	76.7
<del>10734/A01</del>	<del>4.1</del>	<del>0.0</del>	<del>-3.8</del>	<del>51.1</del>
10734/A02	4.1	0.0	-3.8	51.1
10734/A03	10.1	18.5	22.3	87.8
10734/A04	0.6	11.4	11.7	68.0
10734/A05	9.1	22.6	2.9	69.9
10734/A06	-6.4	-6.4	-9.9	46.9
10734/A07	-9.4	15.2	21.9	89.3
10734/A08	0.1	6.8	9.1	71.5
10734/A09	-7.9	27.3	-9.5	88.4
10734/A10	4.4	27.8	26.3	55.4
10734/A11	6.3	12.5	5.5	51.9
10734/B02	8.5	-8.9	-2.9	61.9
10734/B03	21.7	45.1	13.0	90.1
10734/B04	2.8	38.7	14.4	88.4
10734/B05	-2.3	17.8	56.3	67.8

10734/B06	-0.9	54.0	0.2	91.2
10734/B07	9.1	65.5	18.8	93.2
10734/B08	-0.5	19.3	-2.4	56.1
10734/B09	-32.3	34.9	12.6	94.3
10734/B10	15.7	60.7	7.7	82.6
10734/B11	12.6	50.9	-5.5	83.6
10734/C02	-3.9	-6.7	36.0	78.6
10734/C03	-5.6	48.6	24.5	88.2
10734/C04	-37.6	38.1	24.5	90.7
10734/C05	-10.3	9.3	3.8	52.7
10734/C06	-1.7	18.4	-0.2	48.3
10734/C07	-2.7	41.0	32.0	96.8
10734/C08	-34.2	35.1	5.5	93.2
10734/C09	-13.3	36.2	11.3	88.6
10734/C10	10.1	24.4	17.4	11.6
10734/C11	6.3	18.0	9.1	23.9
10734/D02	-11.5	5.2	6.4	46.0
10734/D03	17.4	19.6	24.1	78.6
10734/D04	6.1	-10.7	13.5	46.9
10734/D05	2.4	-9.6	8.2	55.0
10734/D06	0.0	1.3	-9.1	30.6
10734/D07	14.7	51.1	28.1	92.0
10734/D08	2.5	-13.7	2.0	49.8
10734/D09	-11.6	21.0	42.2	88.0
10734/D10	11.1	-4.4	9.9	20.6
10734/D11	9.8	14.6	17.0	33.9
10734/E02	7.9	-10.8	50.1	66.9
10734/E03	26.9	55.0	27.2	99.3
10734/E04	10.7	-7.8	26.7	88.9
10734/E05	10.6	7.9	17.9	63.6
10734/E06	28.4	6.3	13.5	50.6
10734/E07	27.9	82.4	8.2	100.8
10734/E08	26.6	24.2	13.0	89.1
10734/E09	8.0	73.0	1.1	96.2
10734/E10	18.5	-5.0	29.8	27.9
10734/E11	19.2	-8.0	16.1	67.1
10734/F02	6.2	0.7	10.4	55.0
10734/F03	4.2	24.8	-24.1	86.8
10734/F04	-2.6	3.9	25.0	76.5
10734/F05	9.8	-15.6	-1.1	73.8
10734/F06	11.0	-17.1	-21.4	64.2
10734/F07	6.6	33.7	-5.1	95.7
10734/F08	4.8	-23.6	-6.0	66.3
10734/F09	-3.7	3.1	-17.4	93.9
10734/F10	14.8	-8.3	25.8	44.8
10734/F11	13.3	-15.6	16.1	47.3
10734/G02	1.5	3.4	14.8	63.6

10734/G03	18.7	82.8	-3.8	93.4
10734/G04	-1.1	62.9	16.1	72.1
10734/G05	7.4	-0.3	2.9	57.7
10734/G06	16.5	12.5	-18.8	43.1
10734/G07	21.9	51.1	-25.0	96.6
10734/G08	11.6	33.7	0.2	82.2
10734/G09	8.5	21.4	-7.7	84.7
10734/G10	10.8	3.8	9.9	19.3
10734/G11	8.7	4.1	-25.4	20.2
10734/H02	0.5	-11.9	-10.8	48.3
10734/H03	4.6	6.6	8.6	90.3
10734/H04	-1.3	5.9	6.0	64.2
10734/H05	1.6	4.7	-14.4	51.1
10734/H06	2.6	-32.2	-26.3	32.7
10734/H07	1.4	6.6	-6.4	84.9
10734/H08	-2.2	2.9	2.9	64.8
10734/H09	-2.2	-4.2	-19.2	78.4
10734/H10	3.9	-12.6	-17.9	23.5
10734/H11	9.9	-8.5	-17.9	28.7
10735/A02	-13.4	14.3	14.3	26.9
10735/A03	-1.0	28.8	21.9	53.0
10735/A04	-20.8	5.0	18.8	48.0
10735/A05	-12.2	41.5	0.9	46.1
10735/A06	-8.5	24.9	4.7	58.9
10735/A07	-1.3	18.7	0.5	61.9
10735/A08	-19.6	10.9	5.3	50.8
10735/A09	-6.3	13.0	1.9	19.2
10735/A10	2.2	10.2	-0.2	41.4
10735/A11	2.2	3.3	5.7	24.5
10735/B02	1.1	39.1	22.6	72.4
10735/B03	-14.3	42.9	16.4	73.3
10735/B04	6.1	49.2	2.9	79.0
10735/B05	7.4	61.6	17.4	83.7
10735/B06	17.5	49.4	14.0	82.7
10735/B07	-5.9	47.7	0.5	56.0
10735/B08	1.6	24.5	9.8	53.4
10735/B09	15.9	39.8	-0.5	46.8
10735/B10	9.2	30.1	3.6	73.3
10735/B11	15.7	52.4	-8.8	69.0
10735/C02	0.1	1.6	4.7	27.7
10735/C03	0.9	8.0	4.3	66.2
10735/C04	17.2	5.8	12.9	75.8
10735/C05	11.2	14.5	20.5	59.4
10735/C06	18.2	8.5	25.0	47.0
10735/C07	9.6	-4.9	11.9	49.1
10735/C08	10.1	-11.3	-2.6	49.8
10735/C09	24.5	-22.1	-2.6	24.1

10735/C10	21.0	-14.4	4.0	37.8
10735/C11	18.6	-6.4	-2.9	14.1
10735/D02	0.9	20.3	11.6	32.6
10735/D03	4.5	7.5	12.9	41.2
10735/D04	9.1	3.8	8.5	25.6
10735/D05	29.5	23.0	20.5	33.7
10735/D06	16.2	8.0	14.7	36.9
10735/D07	21.6	-17.6	3.6	33.7
10735/D08	21.6	-1.5	-5.7	25.6
10735/D09	22.6	-0.3	6.7	23.0
10735/D10	15.1	46.5	3.3	35.0
10735/D11	25.1	-16.5	0.5	18.5
10735/E02	-2.0	16.7	14.7	13.2
10735/E03	5.1	18.9	16.0	71.8
10735/E04	12.2	14.3	91.6	85.2
10735/E05	14.7	30.6	47.8	74.8
10735/E06	23.8	8.7	32.3	33.3
10735/E07	16.1	27.4	57.1	64.5
10735/E08	14.4	10.2	25.4	35.7
10735/E09	29.6	-3.9	37.1	11.3
10735/E10	10.2	19.1	27.1	41.8
10735/E11	21.9	10.1	11.9	7.2
10735/F02	2.1	19.8	6.0	31.2
10735/F03	11.0	19.1	7.8	36.1
10735/F04	16.4	10.6	40.5	41.6
10735/F05	30.2	5.5	37.1	26.4
10735/F06	16.7	13.0	20.9	39.5
10735/F07	34.0	28.9	19.2	39.7
10735/F08	10.7	9.4	13.3	18.5
10735/F09	40.2	0.0	19.8	7.0
10735/F10	40.0	15.7	13.3	13.0
10735/F11	34.6	14.8	4.0	16.6
10735/G02	5.1	23.7	7.1	26.0
10735/G03	6.8	30.3	6.4	24.3
10735/G04	15.6	22.8	11.6	28.8
10735/G05	8.8	16.7	13.6	22.2
10735/G06	18.5	2.1	12.9	36.1
10735/G07	17.6	4.6	12.6	37.1
10735/G08	10.9	1.6	9.8	29.9
10735/G09	15.9	19.8	2.2	16.8
10735/G10	6.8	4.5	-8.8	37.8
10735/G11	10.1	2.9	-5.3	23.0
10735/H02	14.5	3.6	-4.7	29.2
10735/H03	7.4	-1.0	1.2	40.8
10735/H04	12.8	-9.3	1.2	42.9
10735/H05	29.5	-0.3	9.1	49.8
10735/H06	25.9	-14.2	6.4	57.2

10735/H07	21.4	3.8	-0.9	48.5
10735/H08	29.1	6.8	-2.6	59.2
10735/H09	20.6	-10.7	6.4	22.4
10735/H10	24.0	-16.3	-0.2	29.9
10735/H11	28.3	-4.2	1.9	22.8
10736/A02	-6.0	7.7	24.2	72.5
10736/A03	5.7	24.2	31.6	42.6
10736/A04	-13.0	14.1	13.2	75.2
10736/A05	-19.4	80.1	8.4	73.6
10736/A06	-18.2	34.4	32.1	69.7
10736/A07	-12.6	30.2	8.4	55.2
10736/A08	-13.4	27.6	11.0	58.7
10736/A09	-8.7	20.0	-6.5	69.7
10736/A10	-11.0	-0.1	5.8	65.0
10736/A11	-12.4	-29.3	-5.6	46.1
10736/B02	1.0	-38.8	-10.0	73.6
10736/B03	11.3	-51.7	63.2	65.5
10736/B04	3.0	-9.0	11.9	65.5
10736/B05	-0.5	14.9	-3.0	63.9
10736/B06	3.8	12.6	20.7	60.6
10736/B07	4.0	8.4	20.7	87.2
10736/B08	5.0	8.4	-0.4	59.3
10736/B09	8.0	-3.5	7.1	55.2
10736/B10	2.5	15.6	1.8	52.5
10736/B11	7.3	-3.7	-15.3	47.0
10736/C02	-0.9	-47.1	2.7	50.1
10736/C03	6.5	0.3	25.5	9.9
10736/C04	2.8	90.2	8.4	49.0
10736/C05	4.6	16.8	16.7	44.6
10736/C06	6.2	4.8	26.4	45.2
10736/C07	4.4	-8.1	14.1	55.6
10736/C08	3.1	-0.5	1.4	49.2
10736/C09	11.2	4.6	-9.6	27.9
10736/C10	1.1	-0.3	1.4	18.7
10736/C11	7.2	-4.5	0.5	11.0
10736/D02	5.8	1.8	-10.5	44.4
10736/D03	5.4	-3.7	14.5	14.7
10736/D04	4.3	24.9	15.0	8.1
10736/D05	15.2	-7.9	3.6	3.9
10736/D06	12.2	29.7	19.8	14.7
10736/D07	7.0	47.1	4.4	15.4
10736/D08	11.0	90.9	1.8	13.0
10736/D09	8.5	66.8	-6.5	14.1
10736/D10	-11.6	10.5	-2.1	16.9
10736/D11	12.5	51.7	-4.3	22.6
10736/E02	8.2	2.0	21.5	81.5
10736/E03	17.7	90.2	96.1	33.0

10736/E04	22.6	-17.2	24.6	61.8
10736/E05	30.2	17.0	18.5	57.6
10736/E06	20.1	47.3	10.6	66.6
10736/E07	15.3	-26.7	18.5	45.9
10736/E08	19.3	-47.3	7.9	52.3
10736/E09	14.1	-40.1	-0.4	53.8
10736/E10	27.2	-24.0	26.8	37.8
10736/E11	20.5	-74.1	0.9	64.4
10736/F02	23.9	-4.5	-14.4	69.4
10736/F03	16.6	94.0	-3.0	23.9
10736/F04	16.5	-21.7	3.6	45.2
10736/F05	15.1	-6.0	-4.8	19.8
10736/F06	14.5	25.1	12.3	49.0
10736/F07	16.6	-12.1	-4.3	10.7
10736/F08	7.4	-2.8	-20.1	-0.2
10736/F09	24.0	6.3	2.7	40.2
10736/F10	7.7	-0.7	11.0	65.3
10736/F11	3.7	-23.4	4.4	25.2
10736/G02	-7.2	-4.5	-5.2	48.3
10736/G03	4.5	23.0	1.4	0.6
10736/G04	13.0	-35.0	-8.3	-6.6
10736/G05	2.3	-12.1	-9.2	0.0
10736/G06	5.9	18.9	5.3	1.3
10736/G07	9.4	-74.8	-14.8	-0.2
10736/G08	-0.1	-9.2	-9.2	6.6
10736/G09	-2.1	12.4	-3.5	16.2
10736/G10	6.0	-4.5	-7.4	5.7
10736/G11	0.0	-6.4	-1.7	10.3
10736/H02	6.1	-32.0	-6.1	62.8
10736/H03	15.1	-1.4	2.2	27.7
10736/H04	14.0	-4.3	-10.9	27.2
10736/H05	16.3	-28.9	-10.0	21.1
10736/H06	15.5	12.6	9.3	27.4
10736/H07	17.8	52.2	-21.9	31.0
10736/H08	15.8	-20.2	-17.9	33.4
10736/H09	13.2	35.7	-14.8	32.1
10736/H10	2.1	45.6	-21.0	32.1
10736/H11	17.6	11.1	-12.7	41.5
10737/A02	-5.5	37.3	6.6	53.2
10737/A03	-1.2	12.8	38.8	58.9
10737/A04	-0.4	29.4	23.7	63.5
10737/A05	-2.0	26.4	21.7	58.9
10737/A06	-20.3	37.3	15.7	57.1
10737/A07	3.4	25.3	7.0	30.1
10737/A08	4.9	35.8	1.0	28.3
10737/A09	-10.1	36.0	18.9	47.9
10737/A10	6.0	10.9	-3.8	15.5

10737/A11	6.2	10.8	28.1	25.3
10737/B02	-3.0	-34.0	-28.9	85.0
10737/B03	7.0	-34.9	29.7	86.3
10737/B04	-8.2	7.1	12.5	88.9
10737/B05	-4.6	17.4	19.7	89.5
10737/B06	3.6	22.5	20.1	84.7
10737/B07	10.5	18.1	18.9	82.5
10737/B08	12.2	15.4	-0.6	84.1
10737/B09	17.5	26.4	-14.1	77.0
10737/B10	17.1	-7.3	-10.2	84.7
10737/B11	12.8	-9.9	-10.2	78.8
10737/C02	-2.9	-22.0	-2.2	30.6
10737/C03	10.1	-0.7	7.0	52.5
10737/C04	-20.1	14.4	25.7	82.0
10737/C05	-3.3	13.3	12.5	81.8
10737/C06	8.7	29.0	7.8	38.6
10737/C07	1.6	27.9	8.6	57.5
10737/C08	8.9	16.3	14.5	54.1
10737/C09	8.4	13.0	-1.8	27.6
10737/C10	16.0	-15.6	6.6	60.0
10737/C11	13.3	-5.6	32.5	34.0
10737/D02	10.6	-14.7	-4.2	27.8
10737/D03	12.1	-21.5	-5.8	38.6
10737/D04	12.0	27.7	9.4	33.5
10737/D05	8.9	17.9	2.2	41.8
10737/D06	13.0	33.8	-10.2	37.4
10737/D07	12.9	16.1	-5.0	37.0
10737/D08	15.3	5.6	3.0	42.0
10737/D09	13.9	13.7	1.0	36.0
10737/D10	23.2	-15.0	7.0	24.8
10737/D11	17.2	-2.3	5.4	43.4
10737/E02	14.3	6.7	12.9	53.0
10737/E03	17.9	-4.5	39.2	13.4
10737/E04	16.1	15.4	29.7	79.3
10737/E05	14.9	-8.6	33.3	80.9
10737/E06	11.1	-14.1	26.5	57.8
10737/E07	20.1	-12.3	28.1	43.1
10737/E08	21.3	-7.8	35.6	61.9
10737/E09	11.9	-0.7	25.7	21.2
10737/E10	18.9	-4.2	30.9	49.3
10737/E11	18.3	-33.4	38.0	24.8
10737/F02	15.1	21.4	9.0	67.4
10737/F03	16.3	-3.1	7.8	28.0
10737/F04	12.2	-23.3	3.8	62.8
10737/F05	18.4	-24.0	1.0	67.1
10737/F06	12.3	-13.7	11.3	62.8
10737/F07	19.1	-25.5	12.9	33.3



10737/F08	20.7	28.3	9.8	76.1
10737/F09	15.4	23.5	9.8	76.5
10737/F10	26.1	14.6	11.0	78.6
10737/F11	31.6	-0.7	16.5	75.6
10737/G02	8.7	12.4	-5.8	32.2
10737/G03	13.6	-0.5	21.7	37.4
10737/G04	12.1	-19.3	12.1	49.1
10737/G05	16.4	-41.4	16.1	53.2
10737/G06	12.8	-43.4	-10.2	50.7
10737/G07	20.3	-25.0	24.1	41.8
10737/G08	16.4	30.8	13.7	31.2
10737/G09	15.2	23.6	8.2	37.9
10737/G10	13.3	17.2	-0.2	22.8
10737/G11	11.7	2.8	5.0	35.1
10737/H02	3.1	-17.2	-18.1	42.9
10737/H03	3.2	-22.6	-21.3	46.1
10737/H04	11.6	-17.6	-21.3	63.0
10737/H05	9.9	-17.4	-6.2	76.5
10737/H06	5.8	-31.0	-1.8	28.7
10737/H07	15.5	17.2	-17.7	51.8
10737/H08	10.0	-36.6	-26.9	28.0
10737/H09	5.5	-15.9	-11.7	38.1
10737/H10	10.5	0.3	-12.9	51.6
10737/H11	14.5	4.5	-16.5	31.7
10738/A02	-14.2	16.7		10.0
10738/A03	12.8	40.5		20.7
10738/A04	-16.2	-17.5		55.9
10738/A05	-24.5	33.6		33.1
10738/A06	77.3	54.9		95.8
10738/A07	-22.1	4.3		72.7
10738/A08	-9.3	6.0		12.2
10738/A09	-9.8	17.0		20.2
10738/A10	-8.5	-0.9		35.7
10738/A11	-7.5	4.5		41.7
10738/B02	-8.5	-24.4		78.7
10738/B03	-1.2	19.2		74.0
10738/B04	55.0	51.2		70.7
10738/B05	-13.1	57.6		67.6
10738/B06	-44.1	22.9		83.6
10738/B07	-22.7	28.7		66.7
10738/B08	-0.7	33.9		70.9
10738/B09	-6.2	20.9		79.4
10738/B10	14.3	37.3		70.7
10738/B11	8.8	18.0		75.4
10738/C02	-0.1	-30.5		4.3
10738/C03	28.0	8.2		22.7
10738/C04	84.2	43.7		53.7

10738/C05	-4.4	18.4	34.2
10738/C06	-68.1	28.7	92.2
10738/C07	-7.4	-19.0	51.2
10738/C08	-7.4	-11.9	39.5
10738/C09	4.5	31.9	8.9
10738/C10	-2.5	5.2	3.2
10738/C11	8.4	-1.1	12.0
10738/D02	2.8	21.4	15.6
10738/D03	13.6	47.6	16.0
10738/D04	-13.1	7.4	32.2
10738/D05	-12.5	4.3	42.4
10738/D06	-26.7	32.4	96.0
10738/D07	10.3	-8.7	68.3
10738/D08	11.9	0.6	37.7
10738/D09	9.4	12.1	22.7
10738/D10	15.4	-12.4	25.3
10738/D11	10.4	-13.1	4.3
10738/E02	3.6	56.1	3.8
10738/E03	7.8	82.6	21.1
10738/E04	-11.5	13.1	64.1
10738/E05	-4.8	52.0	61.0
10738/E06	10.1	15.8	92.4
10738/E07	43.4	57.1	89.3
10738/E08	12.8	43.2	52.6
10738/E09	21.2	35.3	18.0
10738/E10	5.1	34.1	5.8
10738/E11	10.2	15.8	11.8
10738/F02	15.0	13.1	66.1
10738/F03	9.0	45.6	20.0
10738/F04	-32.3	-6.5	61.4
10738/F05	3.3	51.5	33.5
10738/F06	-12.6	-19.5	86.7
10738/F07	6.4	9.1	52.3
10738/F08	16.8	15.5	60.5
10738/F09	1.7	0.1	28.9
10738/F10	9.5	-4.8	47.9
10738/F11	15.8	-14.8	52.6
10738/G02	-10.5	19.9	16.9
10738/G03	-4.1	31.9	32.8
10738/G04	-57.2	12.1	42.6
10738/G05	4.0	27.3	27.3
10738/G06	-52.4	-8.2	86.5
10738/G07	-19.3	-1.9	40.4
10738/G08	-15.2	23.6	36.8
10738/G09	4.1	16.7	16.9
10738/G10	-17.0	26.5	12.5
10738/G11	-8.1	19.4	22.2

10738/H02	-14.6	-52.0		35.3
10738/H03	-6.2	16.7		29.5
10738/H04	-17.9	-7.0		72.9
10738/H05	-17.9	5.5		73.6
10738/H06	-44.8	-53.8		93.8
10738/H07	-17.4	-13.4		77.2
10738/H08	-12.7	-12.1		20.7
10738/H09	-6.5	1.6		52.3
10738/H10	1.7	11.4		27.7
10738/H11	-4.1	-13.4		24.9
10739/A02	1.2	-0.0	21.7101226	41.8
10739/A03	2.9	5.1	15.40327885	37.4
10739/A04	-8.2	-6.3	23.16556031	45.2
10739/A05	-11.0	10.7	15.88841512	36.5
10739/A06	7.4	-5.5	17.8289891	70.1
10739/A07	4.1	65.6	34.80897527	99.9
10739/A08	-25.5	6.2	3.759849434	39.9
10739/A09	-9.1	26.9	-0.60643479	60.4
10739/A10	-2.5	20.7	-1.091571056	81.2
10739/A11	3.9	-8.7	1.819289913	82.8
10739/B02	2.1	18.1	5.215287147	68.1
10739/B03	3.5	9.6	1.819289913	62.4
10739/B04	13.2	17.5	19.76956308	65.1
10739/B05	4.1	32.0	4.730136423	74.0
10739/B06	9.3	9.2	6.670710403	68.1
10739/B07	1.1	59.4	19.76956308	96.7
10739/B08	6.5	19.8	-0.121284066	65.8
10739/B09	-15.4	11.9	74.10551883	63.5
10739/B10	-10.1	-2.1	-16.13098325	70.6
10739/B11	12.5	-4.2	-9.824139504	84.9
10739/C02	-10.8	-1.7	10.5518439	34.7
10739/C03	16.4	18.3	10.06670764	10.9
10739/C04	21.8	1.5	19.28441235	-3.6
10739/C05	5.6	-1.7	31.41297803	34.7
10739/C06	17.7	-17.0	33.83868828	56.1
10739/C07	-14.5	34.7	44.51182348	93.0
10739/C08	4.8	-1.7	11.03699463	9.1
10739/C09	10.0	-2.7	105.6397809	76.3
10739/C10	-7.1	-7.0	-18.55670795	66.3
10739/C11	70.6	-17.0	9.096420648	61.0
10739/D02	25.6	2.6	17.8289891	29.0
10739/D03	-18.3	24.7	14.43299186	15.9
10739/D04	11.8	-6.4	7.155846668	11.1
10739/D05	12.2	-10.6	-6.913278535	30.0
10739/D06	9.0	-19.8	-43.78411185	59.2
10739/D07	-5.1	21.1	18.79927609	86.0
10739/D08	14.3	-16.8	5.700423413	5.2

10739/D09	-32.8	-15.1	4.730136423	66.7
10739/D10	14.3	-7.6	12.97756861	20.4
10739/D11	13.8	15.2	3.759849434	65.8
10739/E02	26.7	-8.3	18.31412536	30.0
10739/E03	-119.0	4.9	2.789562444	-3.4
10739/E04	17.7	-35.5	5.215287147	-15.2
10739/E05	28.0	-11.3	10.5518439	8.9
10739/E06	34.3	33.5	72.65008834	66.3
10739/E07	10.0	79.6	48.39296421	94.0
10739/E08	17.2	-17.4	21.7101226	16.1
10739/E09	24.5	15.2	18.31412536	33.8
10739/E10	11.2	17.5	25.59127055	71.9
10739/E11	15.3	-23.4	15.88841512	76.9
10739/F02	25.5	-3.6	6.185574137	50.8
10739/F03	24.5	-10.8	-7.398429259	38.8
10739/F04	26.3	-7.0	-4.002432025	30.4
10739/F05	8.7	-16.4	-4.487568291	-5.4
10739/F06	13.7	-15.3	9.096420648	56.3
10739/F07	0.6	62.4	23.65069658	100.5
10739/F08	7.0	-19.1	9.096420648	13.4
10739/F09	15.6	-19.6	3.274713168	-7.0
10739/F10	12.3	-16.8	4.245000158	40.4
10739/F11	11.9	-38.5	0.849002923	40.9
10739/G02	5.9	-5.1	-12.24984975	12.9
10739/G03	1.9	2.4	-6.913278535	9.3
10739/G04	4.5	-12.3	-3.517281301	4.1
10739/G05	10.7	-23.0	-5.942991546	27.7
10739/G06	14.0	-31.2	-6.42814227	27.7
10739/G07	-4.9	10.0	10.06670764	92.6
10739/G08	15.0	-18.5	1.334139189	20.9
10739/G09	3.1	-39.8	13.94784114	46.1
10739/G10	-2.0	-38.1	-0.60643479	36.5
10739/G11	9.8	-23.2	7.640997392	56.7
10739/H02	2.2	-12.3	-18.55670795	26.6
10739/H03	1.6	10.0	-19.52698048	10.4
10739/H04	9.9	-21.9	-14.19042373	-2.7
10739/H05	5.3	-8.3	-4.972704556	20.0
10739/H06	35.6	-22.1	-17.10127024	42.2
10739/H07	-1.4	10.9	14.91812813	93.7
10739/H08	4.0	-28.5	-3.517281301	22.9
10739/H09	10.0	-44.2	-6.42814227	45.6
10739/H10	15.0	-26.6	-13.22013674	62.4
10739/H11	-7.6	49.9	4.245000158	75.8
10740/A02	5.7	-2.4		56.3
10740/A03	4.2	8.2		77.8
10740/A04	1.3	5.2		48.2
10740/A05	-13.1	30.3		79.5

10740/A06	-8.7	13.1		48.5
10740/A07	-18.3	18.7		54.9
10740/A08	-18.3	-7.9		43.2
10740/A09	-15.7	-9.1		40.1
10740/A10	-7.7	21.9		45.1
10740/A11	-3.5	26.0		30.3
10740/B02	-17.0	46.1		79.2
10740/B03	-9.3	40.1		84.8
10740/B04	-0.3	36.9		76.7
10740/B05	-11.6	30.7		82.3
10740/B06	-5.9	44.4		68.9
10740/B07	-8.5	48.9		73.7
10740/B08	6.6	34.8		65.0
10740/B09	0.8	47.7		71.1
10740/B10	11.8	39.9		58.0
10740/B11	0.7	48.1		68.6
10740/C02	-5.9	15.6		45.1
10740/C03	-129.3	7.2		63.6
10740/C04	-3.4	7.8		-4.9
10740/C05	-19.1	3.5		66.1
10740/C06	-19.1	18.2		49.3
10740/C07	1.1	5.0		44.3
10740/C08	4.6	10.7		28.7
10740/C09	-52.7	28.1		63.3
10740/C10	0.8	21.9		-1.8
10740/C11	6.9	18.7		-10.8
10740/D02	4.1	-0.0		49.9
10740/D03	15.1	-6.9		64.4
10740/D04	-2.0	-1.2		19.4
10740/D05	-6.3	7.4		39.3
10740/D06	9.6	5.8		41.8
10740/D07	-4.5	-3.0		27.3
10740/D08	-6.4	-5.7		30.3
10740/D09	-14.5	14.8		33.1
10740/D10	1.5	9.9		16.1
10740/D11	3.0	19.3		-9.1
10740/E02	9.6	-7.7		48.2
10740/E03	0.2	24.6		66.4
10740/E04	2.0	12.3		41.8
10740/E05	28.7	29.1		75.6
10740/E06	-8.4	-0.0		16.6
10740/E07	34.4	2.7		19.7
10740/E08	39.1	3.1		39.0
10740/E09	89.8	8.6		31.2
10740/E10	11.8	33.0		61.9
10740/E11	17.1	8.8		-16.9
10740/F02	2.8	5.8		59.4

10740/F03	-0.9	16.8		32.8
10740/F04	6.8	11.1		-5.2
10740/F05	-13.5	14.8		52.1
10740/F06	1.3	19.9		25.3
10740/F07	-6.3	-4.2		28.4
10740/F08	-5.0	5.0		35.9
10740/F09	-18.7	11.7		44.3
10740/F10	10.0	9.5		58.3
10740/F11	8.2	5.4		42.9
10740/G02	-2.6	-9.4		55.2
10740/G03	-2.0	19.5		34.8
10740/G04	-5.1	7.6		9.1
10740/G05	-18.6	18.7		30.3
10740/G06	-19.3	-1.2		25.0
10740/G07	0.4	27.9		10.8
10740/G08	-0.5	-9.1		33.4
10740/G09	-8.0	-7.9		37.6
10740/G10	-2.8	1.9		19.4
10740/G11	3.3	-3.4		13.3
10740/H02	-3.7	-9.1		28.7
10740/H03	-9.7	16.0		17.5
10740/H04	6.0	-21.0		30.9
10740/H05	5.8	-4.4		25.6
10740/H06	3.2	4.8		33.4
10740/H07	10.1	-5.3		1.5
10740/H08	11.5	-24.3		28.1
10740/H09	-12.2	-20.6		50.2
10740/H10	0.4	-25.5		43.7
10740/H11	7.4	0.9		17.2

### C. Assay Procedures.

The following *in vitro* assays may be used to determine the level of activity and effect of the different compounds of the present invention on one or more of the PKs. Similar  
5 assays can be designed along the same lines for any PK using techniques well known in the art.

The cellular/catalytic assays described herein are performed in an ELISA format. The general procedure is as follows: a compound is introduced to cells expressing the  
10 test kinase, either naturally or recombinantly, for some period of time after which, if the test kinase is a receptor, a ligand known to activate the receptor is added. The cells are lysed and the lysate is transferred to the wells of an ELISA plate previously coated with a specific  
15 antibody recognizing the substrate of the enzymatic phosphorylation reaction. Non-substrate components of the cell lysate are washed away and the amount of phosphorylation on the substrate is detected with an antibody specifically recognizing phosphotyrosine compared  
20 with control cells that were not contacted with a test compound.

The cellular/biologic assays described herein measure the amount of DNA made in response to activation of a test kinase, which is a general measure of a proliferative  
25 response. The general procedure for this assay is as follows: a compound is introduced to cells expressing the test kinase, either naturally or recombinantly, for some period of time after which, if the test kinase is a receptor, a ligand known to activate the receptor is added.  
30 After incubation at least overnight, a DNA labeling reagent such as Bromodeoxy-uridine (BrdU) or 3H-thymidine is added.

The amount of labeled DNA is detected with either an anti-BrdU antibody or by measuring radioactivity and is compared to control cells not contacted with a test compound.

5    1. Cellular/Catalytic Assays

Enzyme linked immunosorbent assays (ELISA) may be used to detect and measure the presence of PK activity. The ELISA may be conducted according to known protocols which are described in, for example, Voller, et al., 1980, 10 "Enzyme-Linked Immunosorbent Assay," In: Manual of Clinical Immunology, 2d ed., edited by Rose and Friedman, pp 359-371 Am. Soc. Of Microbiology, Washington, D.C.

The disclosed protocol may be adapted for determining activity with respect to a specific PK. For example, the 15 preferred protocols for conducting the ELISA experiments for specific PKs is provided below. Adaptation of these protocols for determining a compound's activity for other members of the RTK family, as well as for CTKs and STKs, is well within the scope of knowledge of those skilled in the 20 art.

a. FLK-1

An ELISA assay was conducted to measure the kinase activity of the FLK-1 receptor and more specifically, the inhibition or activation of TK activity on the FLK-1 25 receptor. Specifically, the following assay was conducted to measure kinase activity of the FLK-1 receptor in cells genetically engineered to express Flk-1.

Materials And Methods.

Materials. The following reagents and supplies were 30 used:



- a. Corning 96-well ELISA plates (Corning Catalog No. 25805-96);
- b. Cappel goat anti-rabbit IgG (catalog no. 55641);
- c. PBS (Gibco Catalog No. 450-1300EB);
- 5 d. TBSW Buffer (50 mM Tris (pH 7.2), 150 mM NaCl and 0.1% Tween-20);
- e. Ethanolamine stock (10% ethanolamine (pH 7.0), stored at 4°C);
- f. HNTG buffer (20mM HEPES buffer (pH 7.5), 150mM  
10 NaCl, 0.2% Triton X-100, and 10% glycerol);
- g. EDTA (0.5 M (pH 7.0) as a 100X stock);
- h. Sodium orthovanadate (0.5 M as a 100X stock);
- i. Sodium pyrophosphate (0.2 M as a 100X stock);
- j. NUNC 96 well V bottom polypropylene plates  
15 (Applied Scientific Catalog No. AS-72092);
- k. NIH3T3 C7#3 Cells (FLK-1 expressing cells);
- l. DMEM with 1X high glucose L-Glutamine (catalog No. 11965-050);
- m. FBS, Gibco (catalog no. 16000-028);
- 20 n. L-glutamine, Gibco (catalog no. 25030-016);
- o. VEGF, PeproTech, Inc. (catalog no. 100-20) (kept as 1 µg/100 µl stock in Milli-Q dH<sub>2</sub>O and stored at -20°C);
- p. Affinity purified anti-FLK-1 antiserum;
- q. UB40 monoclonal antibody specific for  
25 phosphotyrosine (see, Fendley, et al., 1990, Cancer Research 50:1550-1558);
- r. EIA grade Goat anti-mouse IgG-POD (BioRad catalog no. 172-1011);
- s. 2,2-azino-bis(3-ethylbenz-thiazoline-6-sulfonic  
30 acid (ABTS) solution (100mM citric acid (anhydrous), 250 mM Na<sub>2</sub>HPO<sub>4</sub> (pH 4.0), 0.5 mg/ml ABTS (Sigma catalog no. A-1888)),

solution should be stored in dark at 4°C until ready for use;

t. H<sub>2</sub>O<sub>2</sub> (30% solution) (Fisher catalog no. H325);

u. ABTS/H<sub>2</sub>O<sub>2</sub> (15ml ABTS solution, 2 µl H<sub>2</sub>O<sub>2</sub>) prepared 5 minutes before use and left at room temperature;

v. 0.2 M HCl stock in H<sub>2</sub>O;

w. dimethylsulfoxide (100%) (Sigma Catalog No. D-8418); and

y. Trypsin-EDTA (Gibco BRL Catalog No. 25200-049).

10 Protocol. The following protocol was used for conducting the assay:

1. Coat Corning 96-well ELISA plates with 1.0µg per well Cappel Anti-rabbit IgG antibody in 0.1M Na<sub>2</sub>CO<sub>3</sub> pH 9.6. Bring final volume to 150 µl per well. Coat plates overnight at 4°C. Plates can be kept up to two weeks when stored at 4°C.

2. Grow cells in Growth media (DMEM, supplemented with 2.0mM L-Glutamine, 10% FBS) in suitable culture dishes until confluent at 37°C, 5% CO<sub>2</sub>.

20 3. Harvest cells by trypsinization and seed in Corning 25850 polystyrene 96-well round bottom cell plates, 25,000 cells/well in 200µl of growth media.

4. Grow cells at least one day at 37°C, 5% CO<sub>2</sub>.

5. Wash cells with D-PBS 1X.

25 6. Add 200µl/well of starvation media (DMEM, 2.0mM l-Glutamine, 0.1% FBS). Incubate overnight at 37°C, 5% CO<sub>2</sub>.

7. Dilute Compounds 1:20 in polypropylene 96 well plates using starvation media. Dilute dimethylsulfoxide 1:20 for use in control wells.

30 8. Remove starvation media from 96 well cell culture plates and add 162 µl of fresh starvation media to each well.

9. Add 18 $\mu$ l of 1:20 diluted Compound dilution (from step 7) to each well plus the 1:20 dimethylsulfoxide dilution to the control wells (+/- VEGF), for a final dilution of 1:200 after cell stimulation. Final dimethylsulfoxide is 0.5%. Incubate the plate at 37°C, 5% CO<sub>2</sub> for two hours.

10. Remove unbound antibody from ELISA plates by inverting plate to remove liquid. Wash 3 times with TBSW + 0.5% ethanolamine, pH 7.0. Pat the plate on a paper towel to remove excess liquid and bubbles.

11. Block plates with TBSW + 0.5% Ethanolamine, pH 7.0, 150  $\mu$ l per well. Incubate plate thirty minutes while shaking on a microtiter plate shaker.

12. Wash plate 3 times as described in step 10.

13. Add 0.5 $\mu$ g/well affinity purified anti-FLU-1 polyclonal rabbit antiserum. Bring final volume to 150 $\mu$ l/well with TBSW + 0.5% ethanolamine pH 7.0. Incubate plate for thirty minutes while shaking.

14. Add 180  $\mu$ l starvation medium to the cells and stimulate cells with 20 $\mu$ l/well 10.0mM sodium ortho vanadate and 500 ng/ml VEGF (resulting in a final concentration of 1.0mM sodium ortho vanadate and 50ng/ml VEGF per well) for eight minutes at 37°C, 5% CO<sub>2</sub>. Negative control wells receive only starvation medium.

15. After eight minutes, media should be removed from the cells and washed one time with 200 $\mu$ l/well PBS.

16. Lyse cells in 150 $\mu$ l/well HNTG while shaking at room temperature for five minutes. HNTG formulation includes sodium ortho vanadate, sodium pyrophosphate and EDTA.

17. Wash ELISA plate three times as described in step 10.

18. Transfer cell lysates from the cell plate to ELISA plate and incubate while shaking for two hours. To transfer  
5 cell lysate pipette up and down while scrapping the wells.

19. Wash plate three times as described in step 10.

20. Incubate ELISA plate with 0.02µg/well UB40 in TBSW + 05% ethanolamine. Bring final volume to 150µl/well. Incubate while shaking for 30 minutes.

10 21. Wash plate three times as described in step 10.

22. Incubate ELISA plate with 1:10,000 diluted EIA grade goat anti-mouse IgG conjugated horseradish peroxidase in TBSW + 0.5% ethanolamine, pH 7.0. Bring final volume to 150µl/well. Incubate while shaking for thirty minutes.

15 23. Wash plate as described in step 10.

24. Add 100 µl of ABTS/H<sub>2</sub>O<sub>2</sub> solution to well. Incubate ten minutes while shaking.

25. Add 100 µl of 0.2 M HCl for 0.1 M HCl final to stop the color development reaction. Shake 1 minute at room  
20 temperature. Remove bubbles with slow stream of air and read the ELISA plate in an ELISA plate reader at 410 nm.

b. HER-2 ELISA

Assay 1: EGF Receptor-HER2 Chimeric Receptor Assay In Whole Cells.

25 HER2 kinase activity in whole EGFR-NIH3T3 cells was measured as described below:

Materials and Reagents. The following materials and reagents were used to conduct the assay:

a. EGF: stock concentration: 16.5 ILM; EGF 201,  
30 TOYOBO, Co., Ltd. Japan.

b. 05-101 (UBI) (a monoclonal antibody recognizing an EGFR extracellular domain).

Anti-phosphotyrosine antibody (anti-Ptyr) (polyclonal) (see, Fendley, et al., supra).

5 d. Detection antibody: Goat anti-rabbit IgG horse radish peroxidase conjugate, TAGO, Inc., Burlingame, CA.

e. TBST buffer:

	Tris-HCl, pH 7.2	50 mM
	NaCl	150 mM
10	Triton X-100	0.1

f. HNTG 5X stock:

	HEPES	0.1 M
	NaCl	0.75 M
	Glycerol	50%
15	Triton X-100	1.0%

g. ABTS stock:

	Citric Acid	100 mM
	Na <sub>2</sub> HPO <sub>4</sub>	250 mM
	HCl, conc.	0.5 pM
20	ABTS*	0.5mg/ml

\*(2,2'-azinobis(3-ethylbenzthiazolinesulfonic acid)).

Keep solution in dark at 4°C until use.

h. Stock reagents of:

	EDTA 100 mM pH 7.0
25	Na <sub>3</sub> VO <sub>4</sub> 0.5 M
	Na <sub>4</sub> (P <sub>2</sub> O <sub>7</sub> ) 0.2 M

Procedure. The following protocol was used:

A. Pre-coat ELISA Plate

30 1. Coat ELISA plates (Corning, 96 well, Cat. #25805-96) with 05-101 antibody at 0.5 g per well in PBS, 100 µl

final volume/well, and store overnight at 4°C. Coated plates are good for up to 10 days when stored at 4°C.

2. On day of use, remove coating buffer and replace with 100 µl blocking buffer (5% Carnation Instant Non-Fat Dry Milk in PBS). Incubate the plate, shaking, at room temperature (about 23°C to 25°C) for 30 minutes. Just prior to use, remove blocking buffer and wash plate 4 times with TBST buffer.

#### B. Seeding Cells

10. 1. An NIH3T3 cell line overexpressing a chimeric receptor containing the EGFR extracellular domain and intracellular HER2 kinase domain can be used for this assay.
2. Choose dishes having 80-90% confluence for the experiment. Trypsinize cells and stop reaction by adding 10% fetal bovine serum. Suspend cells in DMEM medium (10% CS DMEM medium) and centrifuge once at 1500 rpm, at room temperature for 5 minutes.
3. Resuspend cells in seeding medium (DMEM, 0.5% bovine serum), and count the cells using trypan blue.
- 20 Viability above 90% is acceptable. Seed cells in DMEM medium (0.5% bovine serum) at a density of 10,000 cells per well, 100 µl per well, in a 96 well microtiter plate. Incubate seeded cells in 5% CO<sub>2</sub> at 37°C for about 40 hours.

#### C. Assay Procedures

- 25 1. Check seeded cells for contamination using an inverted microscope. Dilute drug stock (10 mg/ml in DMSO) 1:10 in DMEM medium, then transfer 5 µl to a TBST well for a final drug dilution of 1:200 and a final DMSO concentration of 1%. Control wells receive DMSO alone. Incubate in 5% CO<sub>2</sub> at 37°C for two hours.
- 30

2. Prepare EGF ligand: dilute stock EGF in DMEM so that upon transfer of 10  $\mu$ l dilute EGF (1:12 dilution), 100 nM final concentration is attained.

3. Prepare fresh HNTG\* sufficient for 100  $\mu$ l per well;  
5 and place on ice.

HNTG\* (10 ml):

HNTG stock	2.0 ml
milli-Q H <sub>2</sub> O	7.3 ml
EDTA, 100 mM, pH 7.0	0.5 ml
10 Na <sub>3</sub> VO <sub>4</sub> , 0.5 M	0.1 ml
Na <sub>4</sub> (P <sub>2</sub> O <sub>7</sub> ), 0.2 M	0.1 ml

4. After 120 minutes incubation with drug, add prepared SGF ligand to cells, 10  $\mu$ l per well, to a final concentration of 100 nM. Control wells receive DMEM alone.  
15 Incubate, shaking, at room temperature, for 5 minutes.

5. Remove drug, EGF, and DMEM. Wash cells twice with PBS. Transfer HNTG\* to cells, 100  $\mu$ l per well. Place on ice for 5 minutes. Meanwhile, remove blocking buffer from other ELISA plate and wash with TBST as described above.

20 6. With a pipette tip securely fitted to a micropipettor, scrape cells from plate and homogenize cell material by repeatedly aspirating and dispensing the HNTG\* lysis buffer. Transfer lysate to a coated, blocked, and washed ELISA plate. Incubate shaking at room temperature for  
25 one hour.

7. Remove lysate and wash 4 times with TBST. Transfer freshly diluted anti-Ptyr antibody to ELISA plate at 100  $\mu$ l per well. Incubate shaking at room temperature for 30 minutes in the presence of the anti-Ptyr antiserum (1:3000  
30 dilution in TBST).

8. Remove the anti-Ptyr antibody and wash 4 times with TBST. Transfer the freshly diluted TAGO anti-rabbit

IgG antibody to the ELISA plate at 100  $\mu$ l per well. Incubate shaking at room temperature for 30 minutes (anti-rabbit IgG antibody: 1:3000 dilution in TBST).

9. Remove TAGO detection antibody and wash 4 times  
5 with TBST. Transfer freshly prepared ABTS/H<sub>2</sub>O<sub>2</sub> solution to ELISA plate, 100  $\mu$ l per well. Incubate shaking at room temperature for 20 minutes. (ABTS/H<sub>2</sub>O<sub>2</sub> solution: 1.0  $\mu$ l 30% H<sub>2</sub>O<sub>2</sub> in 10 ml ABTS stock).

10. Stop reaction by adding 50  $\mu$ l 5N H<sub>2</sub>SO<sub>4</sub> (optional),  
10 and determine O.D. at 410 nm.

11. The maximal phosphotyrosine signal is determined by subtracting the value of the negative controls from the positive controls. The percent inhibition of phosphotyrosine content for extract-containing wells is then calculated,  
15 after subtraction of the negative controls.

#### c. PDGF-R ELISA

All cell culture media, glutamine, and fetal bovine serum were purchased from Gibco Life Technologies (Grand Island, NY) unless otherwise specified. All cells were  
20 grown in a humid atmosphere of 90-95% air and 5-10% CO<sub>2</sub> at 37°C. All cell lines were routinely subcultured twice a week and were negative for mycoplasma as determined by the Mycotect method (Gibco).

For ELISA assays, cells (U1242, obtained from Joseph  
25 Schlessinger, NYU) were grown to 80-90% confluency in growth medium (MEM with 10% FBS, NEAA, 1 mM NaPyr and 2 mM GLN) and seeded in 96-well tissue culture plates in 0.5% serum at 25,000 to 30,000 cells per well. After overnight incubation in 0.5% serum-containing medium, cells were changed to  
30 serum-free medium and treated with test compound for 2 hr in a 5% CO<sub>2</sub>, 37°C incubator. Cells were then stimulated with



ligand for 5-10 minute followed by lysis with HNTG (20 mM Hepes, 150 mM NaCl, 10% glycerol, 5 mM EDTA, 5 mM  $\text{Na}_3\text{VO}_4$ , 0.2% Triton X-100, and 2 mM NaPyr). Cell lysates (0.5 mg/well in PBS) were transferred to ELISA plates previously  
5 coated with receptor-specific antibody and which had been blocked with 5% milk in TBST (50 mM Tris-HCl pH 7.2, 150 mM NaCl and 0.1% Triton X-100) at room temperature for 30 min. Lysates were incubated with shaking for 1 hour at room temperature. The plates were washed with TBST four times  
10 and then incubated with polyclonal anti-phosphotyrosine antibody at room temperature for 30 minutes. Excess anti-phosphotyrosine antibody was removed by rinsing the plate with TBST four times. Goat anti-rabbit IgG antibody was added to the ELISA plate for 30 min at room temperature  
15 followed by rinsing with TBST four more times. ABTS (100 mM citric acid, 250 mM  $\text{Na}_2\text{HPO}_4$  and 0.5 mg/mL 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid)) plus  $\text{H}_2\text{O}_2$  (1.2 mL 30%  $\text{H}_2\text{O}_2$  to 10 ml ABTS) was added to the ELISA plates to start color development. Absorbance at 410 nm with a reference  
20 wavelength of 630 nm was recorded about 15 to 30 min after ABTS addition.

#### d. IGF-I RECEPTOR ELISA

The following protocol may be used to measure phosphotyrosine level on IGF-I receptor, which indicates  
25 IGF-I receptor tyrosine kinase activity.

Materials And Reagents. The following materials and reagents were used:

a. The cell line used in this assay is 3T3/IGF-1R, a cell line genetically engineered to overexpresses IGF-1  
30 receptor.

196

b. NIH3T3/IGF-1R is grown in an incubator with 5% CO<sub>2</sub> at 37°C. The growth media is DMEM + 10% FBS (heat inactivated)+ 2mM L-glutamine.

c. Affinity purified anti-IGF-1R antibody 17-69.

5

d. D-PBS:

KH<sub>2</sub>PO<sub>4</sub> 0.20 g/l

K<sub>2</sub>HPO<sub>4</sub> 2.16 g/l

KCl 0.20 g/l

NaCl 8.00 g/l (pH 7.2)

10

e. Blocking Buffer: TBST plus 5% Milk (Carnation Instant Non-Fat Dry Milk).

f. TBST buffer:

Tris-HCl 50 mM

NaCl 150mM (pH 7.2/HCl 10N)

15

Triton X-100 0.1%

Stock solution of TBS (10X) is prepared, and Triton X-100 is added to the buffer during dilution.

g. HNTG buffer:

HEPES 20 mM

20

NaCl 150 mM (pH 7.2/HCl 1N)

Glycerol 10%

Triton X-100 0.2%

Stock solution (5X) is prepared and kept at 4°C.

h. EDTA/HCl: 0.5 M pH 7.0 (NaOH) as 100X stock.

25

i. Na<sub>3</sub>VO<sub>4</sub>: 0.5 M as 100X stock and aliquots are kept in -80°C.

j. Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub>: 0.2 M as 100X stock.

k. Insulin-like growth factor-1 from Promega (Cat# G5111).

30

l. Rabbit polyclonal anti-phosphotyrosine antiserum.

m. Goat anti-rabbit IgG, POD conjugate (detection antibody), Tago (Cat. No. 4520, Lot No. 1802): Tago, Inc., Burlingame, CA.

n. ABTS (2,2'-azinobis(3-ethylbenzthiazolinesulfonic acid)) solution:

Citric acid	100 mM
Na <sub>2</sub> HPO <sub>4</sub>	250 mM (pH 4.0/1 N HCl)
ABTS	0.5 mg/ml

ABTS solution should be kept in dark and 4°C. The solution should be discarded when it turns green.

o. Hydrogen Peroxide: 30% solution is kept in the dark and at 4°C.

Procedure. All the following steps are conducted at room temperature unless it is specifically indicated. All ELISA plate washings are performed by rinsing the plate with tap water three times, followed by one TBST rinse. Pat plate dry with paper towels.

A. Cell Seeding:

1. The cells, grown in tissue culture dish (Corning 25020-100) to 80-90% confluence, are harvested with Trypsin-EDTA (0.25%, 0.5 ml/D-100, GIBCO).

2. Resuspend the cells in fresh DMEM + 10% FBS + 2mM L-Glutamine, and transfer to 96-well tissue culture plate (Corning, 25806-96) at 20,000 cells/well (100 µl/well). Incubate for 1 day then replace medium to serum-free medium (90 µl) and incubate in 5% CO<sub>2</sub> and 37°C overnight.

B. ELISA Plate Coating and Blocking:

1. Coat the ELISA plate (Corning 25805-96) with Anti-IGF-1R Antibody at 0.5 µg/well in 100 µl PBS at least 2 hours.
- 5      2. Remove the coating solution, and replace with 100 µl Blocking Buffer, and shake for 30 minutes. Remove the blocking buffer and wash the plate just before adding lysate.

C. Assay Procedures:

- 10      1. The drugs are tested in serum-free condition.
2. Dilute drug stock (in 100% DMSO) 1:10 with DMEM in 96-well poly-propylene plate, and transfer 10 µl/well of this solution to the cells to achieve final drug dilution 1:100, and final DMSO concentration of 1.0%. Incubate the  
15 cells in 5% CO<sub>2</sub> at 37°C for 2 hours.
3. Prepare fresh cell lysis buffer (HNTG\*)

HNTG	2 ml
EDTA	0.1 ml
Na <sub>3</sub> VO <sub>4</sub>	0.1 ml
20      Na <sub>4</sub> (P <sub>2</sub> O <sub>7</sub> )	0.1 ml
H <sub>2</sub> O	7.3 ml
4. After drug incubation for two hours, transfer 10 µl/well of 200nM IGF-1 Ligand in PBS to the cells (Final Conc. = 20 nM), and incubate at 5% CO<sub>2</sub> at 37°C for 10  
25 minutes.
5. Remove media and add 100µl/well HNTG\* and shake for 10 minutes. Look at cells under microscope to see if they are adequately lysed.
6. Use a 12-channel pipette to scrape the cells from  
30 the plate, and homogenize the lysate by repeated aspiration

and dispensing. Transfer all the lysate to the antibody coated ELISA plate, and shake for 1 hour.

7. Remove the lysate, wash the plate, transfer anti-pTyr (1:3,000 with TBST) 100 µl/well, and shake for 30 minutes.

8. Remove anti-pTyr, wash the plate, transfer TAGO (1:3,000 with TBST) 100 µl/well, and shake for 30 minutes.

9. Remove detection antibody, wash the plate, and transfer fresh ABTS/H<sub>2</sub>O<sub>2</sub> (1.2 µl H<sub>2</sub>O<sub>2</sub> to 10 ml ABTS) 100 µl/well to the plate to start color development.

10. Measure OD at 410 nm with a reference wavelength of 630 nm in Dynatec MR5000.

e. EGF Receptor ELISA

EGF Receptor kinase activity in cells genetically engineered to express human EGF-R was measured as described below:

Materials and Reagents. The following materials and reagents were used

a. EGF Ligand: stock concentration = 16.5 µM; EGF 201, TOYOBO, Co., Ltd. Japan.

b. 05-101 (UBI) (a monoclonal antibody recognizing an EGFR extracellular domain).

c. Anti-phosphotyrosine antibody (anti-Ptyr) (polyclonal).

25 d. Detection antibody: Goat anti-rabbit IgG horse radish peroxidase conjugate, TAGO, Inc., Burlingame, CA.

e. TBST buffer:

Tris-HCl, pH 7 50 mM

NaCl 150 mM

30 Triton X-100 0.1

f. HNTG 5X stock:

200

- |    |  |           |
|----|--|-----------|
|    | HEPES  | 0.1 M     |
|    | NaCl   | 0.75 M    |
|    | Glycerol   | 50        |
|    | Triton X-100   | 1.0%      |
| 5  | g. ABTS stock:   |           |
|    | Citric Acid  | 100 mM    |
|    | Na <sub>2</sub> HPO <sub>4</sub>                       | 250 mM    |
|    | HCl, conc.   | 4.0 pH    |
|    | ABTS*  | 0.5 mg/ml |
| 10 | Keep solution in dark at 4°C until used.               |           |
|    | h. Stock reagents of:                                  |           |
|    | EDTA 100 mM pH 7.0                                     |           |
|    | Na <sub>3</sub> VO <sub>4</sub> 0.5 M                  |           |
|    | Na <sub>4</sub> (P <sub>2</sub> O <sub>7</sub> ) 0.2 M |           |
| 15 | Procedure. The following protocol was used:            |           |

A. Pre-coat ELISA Plate

1. Coat ELISA plates (Corning, 96 well, Cat. #25805-96) with 05-101 antibody at 0.5 µg per well in PBS, 150 µl final volume/well, and store overnight at 4°C. Coated plates  
20 are good for up to 10 days when stored at 4°C.

2. On day of use, remove coating buffer and replace with blocking buffer (5% Carnation Instant NonFat Dry Milk in PBS). Incubate the plate, shaking, at room temperature (about 23°C to 25°C) for 30 minutes. Just prior to use,  
25 remove blocking buffer and wash plate 4 times with TBST buffer.

B. Seeding Cells

1. NIH 3T3/C7 cell line (Honegger, et al., Cell 51:199-209, 1987) can be use for this assay.

2. Choose dishes having 80-90% confluence for the experiment. Trypsinize cells and stop reaction by adding 10% CS DMEM medium. Suspend cells in DMEM medium (10% CS DMEM medium) and centrifuge once at 1000 rpm at room temperature for 5 minutes.

3. Resuspend cells in seeding medium (DMEM, 0.5% bovine serum), and count the cells using trypan blue. Viability above 90% is acceptable. Seed cells in DMEM medium (0.5% bovine serum) at a density of 10,000 cells per well, 100  $\mu$ l per well, in a 96 well microtiter plate. Incubate seeded cells in 5% CO<sub>2</sub> at 37°C for about 40 hours.

#### C. Assay Procedures.

1. Check seeded cells for contamination using an inverted microscope. Dilute drug stock (10 mg/ml in DMSO) 1:10 in DMEM medium, then transfer 5  $\mu$ l to a test well for a final drug dilution of 1:200 and a final DMSO concentration of 1%. Control wells receive DMSO alone. Incubate in 5% CO<sub>2</sub> at 37°C for one hour.

2. Prepare EGF ligand: dilute stock EGF in DMEM so that upon transfer of 10  $\mu$ l dilute EGF (1:12 dilution), 25 nM final concentration is attained.

3. Prepare fresh 10 ml HNTG\* sufficient for 100  $\mu$ l per well wherein HNTG\* comprises: HNTG stock (2.0 ml), milli-Q H<sub>2</sub>O (7.3 ml), EDTA, 100 mM, pH 7.0 (0.5 ml), Na<sub>3</sub>VO<sub>4</sub> 0.5 M (0.1 ml) and Na<sub>4</sub>(P<sub>2</sub>O<sub>7</sub>), 0.2 M (0.1 ml).

4. Place on ice.

5. After two hours incubation with drug, add prepared EGF ligand to cells, 10  $\mu$ l per well, to yield a final concentration of 25 nM. Control wells receive DMEM alone. Incubate, shaking, at room temperature, for 5 minutes.

6. Remove drug, EGF, and DMEM. Wash cells twice with PBS. Transfer HNTG\* to cells, 100  $\mu$ l per well. Place on ice for 5 minutes. Meanwhile, remove blocking buffer from other ELISA plate and wash with TBST as described above.

5        7. With a pipette tip securely fitted to a micropipettor, scrape cells from plate and homogenize cell material by repeatedly aspirating and dispensing the HNTG\* lysis buffer. Transfer lysate to a coated, blocked, and washed ELISA plate. Incubate shaking at room temperature for  
10       one hour.

8. Remove lysate and wash 4 times with TBST. Transfer freshly diluted anti-Ptyr antibody to ELISA plate at 100  $\mu$ l per well. Incubate shaking at room temperature for 30 minutes in the presence of the anti-Ptyr antiserum (1:3000  
15       dilution in TBST).

9. Remove the anti-Ptyr antibody and wash 4 times with TBST. Transfer the freshly diluted TAGO 30 anti-rabbit IgG antibody to the ELISA plate at 100  $\mu$ l per well. Incubate shaking at room temperature for 30 minutes (anti-rabbit IgG  
20       antibody: 1:3000 dilution in TBST).

10. Remove detection antibody and wash 4 times with TBST. Transfer freshly prepared ABTS/H<sub>2</sub>O<sub>2</sub> solution to ELISA plate, 100  $\mu$ l per well. Incubate at room temperature for 20 minutes. ABTS/H<sub>2</sub>O<sub>2</sub> solution: 1.2  $\mu$ l 30% H<sub>2</sub>O<sub>2</sub> in 10 ml ABTS  
25       stock.

11. Stop reaction by adding 50  $\mu$ l 5N H<sub>2</sub>SO<sub>4</sub> (optional), and determine O.D. at 410 nm.

12. The maximal phosphotyrosine signal is determined by subtracting the value of the negative controls from the  
30       positive controls. The percent inhibition of phosphotyrosine content for extract-containing wells is then calculated, after subtraction of the negative controls.



f. Met Autophosphorylation Assay - ELISA

This assay determines Met tyrosine kinase activity by analyzing Met protein tyrosine kinase levels on the Met receptor.

5        1. Reagents

      a. HNTG (5X stock solution): Dissolve 23.83 g HEPES and 43.83 g NaCl in about 350 ml dH<sub>2</sub>O. Adjust pH to 7.2 with HCl or NaOH, add 500 ml glycerol and 10 ml Triton X-100, mix, add dH<sub>2</sub>O to 1 L total volume. To make 1 L of 1X working  
10    solution add 200 ml 5X stock solution to 800 ml dH<sub>2</sub>O, check and adjust pH as necessary, store at 4°C.

      b. PBS (Dulbecco's Phosphate-Buffered Saline), Gibco Cat. # 450-1300EB (1X solution).

      c. Blocking Buffer: in 500 ml dH<sub>2</sub>O place 100 g BSA,  
15    12.1 g Tris-pH7.5, 58.44 g NaCl and 10 ml Tween-20, dilute to 1 L total volume.

      d. Kinase Buffer: To 500 ml dH<sub>2</sub>O add 12.1 g TRIS pH7.2, 58.4 g NaCl, 40.7 g MgCl<sub>2</sub> and 1.9 g EGTA; bring to 1 L total volume with dH<sub>2</sub>O.

20        e. PMSF (Phenylmethylsulfonyl fluoride), Sigma Cat. # P-7626, to 435.5 mg, add 100% ethanol to 25 ml total volume, vortex.

      f. ATP (Bacterial Source), Sigma Cat. # A-7699, store powder at -20°C; to make up solution for use, dissolve 3.31  
25    mg in 1 ml dH<sub>2</sub>O.

      g. RC-20H    HRPO    Conjugated    Anti-Phosphotyrosine, Transduction Laboratories Cat. # E120H.

      h. Pierce 1-Step (TM) Turbo TMB-ELISA (3,3',5,5'-tetramethylbenzidine, Pierce Cat. # 34022.

30        i. H<sub>2</sub>SO<sub>4</sub>, add 1 ml conc. (18N) to 35 ml dH<sub>2</sub>O.

- j. TRIS HCL, Fischer Cat. # BP152-5; to 121.14 g of material, add 600 ml MilliQ H<sub>2</sub>O, adjust pH to 7.5 (or 7.2) with HCl, bring volume to 1 L with MilliQ H<sub>2</sub>O.
- k. NaCl, Fischer Cat. # S271-10, make up 5M solution.
- 5 l. Tween-20, Fischer Cat. # S337-500.
- m. Na<sub>3</sub>VO<sub>4</sub>, Fischer Cat. # S454-50, to 1.8 g material add 80 ml MilliQ H<sub>2</sub>O, adjust pH to 10.0 with HCl or NaOH, boil in microwave, cool, check pH, repeat procedure until pH stable at 10.0, add MilliQ H<sub>2</sub>O to 100 ml total volume, make 1  
10 ml aliquots and store at -80°C.
- n. MgCl<sub>2</sub>, Fischer Cat. # M33-500, make up 1M solution.
- o. HEPES, Fischer Cat. # BP310-500, to 200 ml MilliQ H<sub>2</sub>O, add 59.6 g material, adjust pH to 7.5, bring volume to 250 ml total, sterile filter.
- 15 p. Albumin, Bovine (BSA), Sigma Cat. # A-4503, to 30 grams material add sterile distilled water to make total volume of 300 ml, store at 4°C.
- q. TBST Buffer: to approx. 900 ml dH<sub>2</sub>O in a 1 L graduated cylinder add 6.057 g TRIS and 8.766 g NaCl, when  
20 dissolved, adjust pH to 7.2 with HCl, add 1.0 ml Triton X-100 and bring to 1 L total volume with dH<sub>2</sub>O.
- r. Goat Affinity purified antibody Rabbit IgG (whole molecule), Cappel Cat. # 55641.
- s. Anti h-Met (C-28) rabbit polyclonal IgG antibody,  
25 Santa Cruz Chemical Cat. # SC-161.
- t. Transiently Transfected EGFR/Met chimeric cells (EMR) (Komada, et al., Oncogene, 8:2381-2390 (1993)).
- u. Sodium Carbonate Buffer, (Na<sub>2</sub>CO<sub>4</sub>, Fischer Cat. # S495): to 10.6 g material add 800 ml MilliQ H<sub>2</sub>O, when  
30 dissolved adjust pH to 9.6 with NaOH, bring up to 1 L total volume with MilliQ H<sub>2</sub>O, filter, store at 4°C.

## 2. Procedure

All of the following steps are conducted at room temperature unless it is specifically indicated otherwise. All ELISA plate washing is by rinsing 4X with TBST.

### 5 A. EMR Lysis

This procedure can be performed the night before or immediately prior to the start of receptor capture.

1. Quick thaw lysates in a 37°C waterbath with a swirling motion until the last crystals disappear.

10 2. Lyse cell pellet with 1X HNTG containing 1 mM PMSF. Use 3 ml of HNTG per 15 cm dish of cells. Add 1/□ the calculated HNTG volume, vortex the tube for 1 min., add the remaining amount of HNTG, vortex for another min.

15 3. Balance tubes, centrifuge at 10,000x g for 10 min at 4°C.

4. Pool supernatants, remove an aliquot for protein determination.

20 5. Quick freeze pooled sample in dry ice/ethanol bath. This step is performed regardless of whether lysate will be stored overnight or used immediately following protein determination.

6. Perform protein determination using standard bicinchoninic acid (BCA) method (BCA Assay Reagent Kit from Pierce Chemical Cat. # 23225).

### 25 B. ELISA Procedure

1. Coat Corning 96 well ELISA plates with 5 µg per well Goat anti-Rabbit antibody in Carbonate Buffer for a total well volume of 50 µl. Store overnight at 4°C.

30 2. Remove unbound Goat anti-rabbit antibody by inverting plate to remove liquid.

3. Add 150  $\mu$ l of Blocking Buffer to each well. Incubate for 30 min. at room temperature with shaking.
4. Wash 4X with TBST. Pat plate on a paper towel to remove excess liquid and bubbles.
- 5 5. Add 1 $\mu$ g per well of Rabbit anti-Met antibody diluted in TBST for a total well volume of 100  $\mu$ l.
6. Dilute lysate in HNTG (90  $\mu$ g lysate/100 $\mu$ l)
7. Add 100  $\mu$ l of diluted lysate to each well. Shake at room temperature for 60 min.
- 10 8. Wash 4X with TBST. Pat on paper towel to remove excess liquid and bubbles.
9. Add 50  $\mu$ l of 1X lysate buffer per well.
10. Dilute compounds/extracts 1:10 in 1X Kinase Buffer in a polypropylene 96 well plate.
- 15 11. Transfer 5.5  $\mu$ l of diluted drug to ELISA plate wells. Incubate at room temperature with shaking for 20 min.
12. Add 5.5  $\mu$ l of 60  $\mu$ M ATP solution per well. Negative controls do not receive any ATP. Incubate at room temperature for 90 min., with shaking.
- 20 13. Wash 4X with TBST. Pat plate on paper towel to remove excess liquid and bubbles.
14. Add 100  $\mu$ l per well of RC20 (1:3000 dilution in Blocking Buffer). Incubate 30 min. at room temperature with shaking.
- 25 15. Wash 4X with TBST. Pat plate on paper towel to remove excess liquid and bubbles.
16. Add 100  $\mu$ l per well of Turbo-TMB. Incubate with shaking for 30-60 min.
- 30 17. Add 100  $\mu$ l per well of 1M H<sub>2</sub>SO<sub>4</sub> to stop reaction.

18. Read assay on Dynatech MR7000 ELISA reader. Test Filter = 450 nm, reference filter = 410 nm.

g. Biochemical src assay - ELISA

This assay is used to determine src protein kinase activity measuring phosphorylation of a biotinylated peptide as the readout.

1. Materials and Reagents:

a. Yeast transformed with src from Courtneidge Laboratory (Sugen, Inc., Redwood City, California).

10 b. Cell lysates: Yeast cells expressing src are pelleted, washed once with water, re-pelleted and stored at -80°C until use.

c. N-terminus biotinylated EEEYEEYEEEEYEEYEEY is prepared by standard procedures well known to those skilled in the art.

d. DMSO: Sigma, St. Louis, MO.

e. 96 Well ELISA Plate: Corning 96 Well Easy Wash, Modified flat Bottom Plate, Corning Cat. #25805-96.

20 f. NUNC 96-well V-bottom polypropylene plates for dilution of compounds: Applied Scientific Cat. # A-72092.

g. Vecastain ELITE ABC reagent: Vector, Burlingame, CA.

h. Anti-src (327) mab: Schizosaccharomyces Pombe was used to express recombinant Src (Superti-Furga, et al., EMBO J., 12:2625-2634; Superti-Furga, et al., Nature Biochem., 14:600-605). S. Pombe strain SP200 (h-s leul.32 ura4 ade210) was grown as described and transformations were pRSP expression plasmids were done by the lithium acetate method (Superti-Furga, supra). Cells were grown in the presence of

1  $\mu$ M thiamine to repress expression from the nmt1 promoter  
or in the absence of thiamine to induce expression.

i. Monoclonal anti-phosphotyrosine, UBI 05-321 (UB40  
may be used instead).

5 j. Turbo TMB-ELISA peroxidase substrate: Pierce  
Chemical.

2. Buffer Solutions:

a. PBS (Dulbecco's Phosphate-Buffered Saline): GIBCO  
PBS, GIBCO Cat. # 450-1300EB.

10 b. Blocking Buffer: 5% Non-fat milk (Carnation) in  
PBS.

c Carbonate Buffer:  $\text{Na}_2\text{CO}_4$  from Fischer, Cat. #  
S495, make up 100 mM stock solution.

15 d. Kinase Buffer: 1.0 ml (from 1M stock solution)  
 $\text{MgCl}_2$ ; 0.2 ml (from a 1M stock solution)  $\text{MnCl}_2$ ; 0.2 ml (from  
a 1M stock solution) DTT; 5.0 ml (from a 1M stock solution)  
HEPES; 0.1 ml TX-100; bring to 10 ml total volume with  
MilliQ  $\text{H}_2\text{O}$ .

20 e. Lysis Buffer: 5.0 HEPES (from 1M stock solution.);  
2.74 ml NaCl (from 5M stock solution); 10 ml glycerol; 1.0  
ml TX-100; 0.4 ml EDTA (from a 100 mM stock solution); 1.0  
ml PMSF (from a 100 mM stock solution); 0.1 ml  $\text{Na}_3\text{VO}_4$  (from a  
0.1 M stock solution); bring to 100 ml total volume with  
MilliQ  $\text{H}_2\text{O}$ .

25 f. ATP: Sigma Cat. # A-7699, make up 10 mM stock  
solution (5.51 mg/ml).

g TRIS-HCl: Fischer Cat. # BP 152-5, to 600 ml  
MilliQ  $\text{H}_2\text{O}$  add 121.14 g material, adjust pH to 7.5 with HCl,  
bring to 1 L total volume with MilliQ  $\text{H}_2\text{O}$ .

30 h. NaCl: Fischer Cat. # S271-10, Make up 5M stock  
solution with MilliQ  $\text{H}_2\text{O}$ .

Na<sub>3</sub>VO<sub>4</sub>: Fischer Cat. # S454-50; to 80 ml MilliQ H<sub>2</sub>O, add 1.8 g material; adjust pH to 10.0 with HCl or NaOH; boil in a microwave; cool; check pH, repeat pH adjustment until pH remains stable after heating/cooling cycle; bring to 100  
5 ml total volume with MilliQ H<sub>2</sub>O; make 1 ml aliquots and store at -80°C.

j. MgCl<sub>2</sub>: Fischer Cat. # M33-500, make up 1M stock solution with MilliQ H<sub>2</sub>O.

k. HEPES: Fischer Cat. # BP 310-500; too 200 ml  
10 MilliQ H<sub>2</sub>O, add 59.6 g material, adjust pH to 7.5, bring to 250 ml total volume with MilliQ H<sub>2</sub>O, sterile filter (1M stock solution).

l. TBST Buffer: TBST Buffer: To 900 ml dH<sub>2</sub>O add 6.057 g TRIS and 8.766 g NaCl; adjust pH to 7.2 with HCl,  
15 add 1.0 ml Triton-X100; bring to 1 L total volume with dH<sub>2</sub>O.

m. MnCl<sub>2</sub>: Fischer Cat. # M87-100, make up 1M stock solution with MilliQ H<sub>2</sub>O.

n. DTT: Fischer Cat. # BP172-5.

o. TBS (TRIS Buffered Saline): to 900 ml MilliQ H<sub>2</sub>O  
20 add 6.057 g TRIS and 8.777 g NaCl; bring to 1 L total volume with MilliQ H<sub>2</sub>O.

p. Kinase Reaction Mixture: Amount per assay plate (100 wells): 1.0 ml Kinase Buffer, 200 µg GST-□, bring to final volume of 8.0 ml with MilliQ H<sub>2</sub>O.

25 q. Biotin labeled EEEYEEYEEYEEYEEY: Make peptide stock solution (1mM, 2.98 mg/ml) in water fresh just before use.

r. Vectastain ELITE ABC reagent: To prepare 14 ml of working reagent, add 1 drop of reagent A to 15 ml TBST and  
30 invert tube several times to mix. Then add 1 drop of reagent B. Put tube on orbital shaker at room temperature and mix for 30 minutes.

### 3. Procedures:

#### a. Preparation of src coated ELISA plate.

1. Coat ELISA plate with 0.5µg/well anti-src mab in 100 µl of pH 9.6 sodium carbonate buffer at 4°C overnight.
- 5        2. Wash wells once with PBS.
3. Block plate with 0.15 ml 5% milk in PBS for 30 min. at room temperature.
4. Wash plate 5X with PBS.
- 10       5. Add 10 µg/well of src transformed yeast lysates diluted in Lysis Buffer (0.1 ml total volume per well). (Amount of lysate may vary between batches.) Shake plate for 20 minutes at room temperature.

#### b. Preparation of phosphotyrosine antibody-coated ELISA plate.

- 15       1. 4G10 plate: coat 0.5 µg/well 4G10 in 100 µl PBS overnight at 4°C and block with 150 µl of 5% milk in PBS for 30 minutes at room temperature.

#### c. Kinase assay procedure.

- 20       1. Remove unbound proteins from step 1-7, above, and wash plates 5X with PBS.
2. Add 0.08 ml Kinase Reaction Mixture per well (containing 10 µl of 10X Kinase Buffer and 10 µM (final concentration) biotin-EEEEEEEEEEEEEEEE per well diluted in water.
- 25       3. Add 10 µl of compound diluted in water containing 10% DMSO and pre-incubate for 15 minutes at room temperature.
4. Start kinase reaction by adding 10µl/well of 0.05 mM ATP in water (5 µM ATP final).



211

5. Shake ELISA plate for 15 min. at room temperature.
6. Stop kinase reaction by adding 10  $\mu$ l of 0.5 M EDTA per well.
7. Transfer 90  $\mu$ l supernatant to a blocked 4G10
5. coated ELISA plate from section B, above.
8. Incubate for 30 min. while shaking at room temperature.
9. Wash plate 5X with TBST.
10. Incubate with Vectastain ELITE ABC reagent (100
- 10  $\mu$ l/well) for 30 min. at room temperature.
11. Wash the wells 5X with TBST.
12. Develop with Turbo TMB.

#### h. Biochemical lck Assay - ELISA

This assay is used to determine lck protein kinase  
15 activities measuring phosphorylation of GST- $\square$  as the  
readout.

##### 1. Materials and Reagents:

- a. Yeast transformed with lck. Schizosaccharomyces  
Pombe was used to express recombinant Lck (Superti-Furga, et  
20 al., EMBO J, 12:2625-2634; Superti-Furga, et al., Nature  
Biotech., 14:600-605). S. Pombe strain SP200 (h-s leul.32  
ura4 ade210) was grown as described and transformations with  
pRSP expression plasmids were done by the lithium acetate  
method (Superti-Furga, supra). Cells were grown in the  
25 presence of 1  $\mu$ M thiamine to induce expression.
- b. Cell lysates: Yeast cells expressing lck are  
pelleted, washed once in water, re-pelleted and stored  
frozen at -80°C until use.
- c. GST- $\square$ : DNA encoding for GST- $\square$  fusion protein for  
30 expression in bacteria obtained from Arthur Weiss of the

Howard Hughes Medical Institute at the University of California, San Francisco. Transformed bacteria were grown overnight while shaking at 25°C. GST-□ was purified by glutathione affinity chromatography, Pharmacia, Alameda, CA.

- 5 d. DMSO: Sigma, St. Louis, MO.
- e. 96-Well ELISA plate: Corning 96 Well Easy Wash, Modified Flat Bottom Plate, Corning Cat. #25805-96.
- f. NUNC 96-well V-bottom polypropylene plates for dilution of compounds: Applied Scientific Cat. # AS-72092.
- 10 g. Purified Rabbit anti-GST antiserum: Amrad Corporation (Australia) Cat. #90001605.
- h. Goat anti-Rabbit-IgG-HRP: Amersham Cat. # V010301.
- i. Sheep anti-mouse IgG (H+L): Jackson Labs Cat. # 5215-005-003.
- 15 j. Anti-Lck (3A5) mab: Santa Cruz Biotechnology Cat # sc-433.
- k. Monoclonal anti-phosphotyrosine UBI 05-321 (UB40 may be used instead).

## 2. Buffer solutions:

- 20 a. PBS (Dulbecco's Phosphate-Buffered Saline) 1X solution: GIBCO PBS, GIBCO Cat. # 450-1300EB.
- b. Blocking Buffer: 100 g. BSA, 12.1 g. TRIS-pH7.5, 58.44 g NaCl, 10 ml Tween-20, bring up to 1 L total volume with MilliQ H<sub>2</sub>O.
- 25 c. Carbonate Buffer: Na<sub>2</sub>CO<sub>4</sub> from Fischer, Cat. # S495; make up 100 mM solution with MilliQ H<sub>2</sub>O.
- d. Kinase Buffer: 1.0 ml (from 1M stock solution) MgCl<sub>2</sub>; 0.2 ml (from a 1M stock solution) MnCl<sub>2</sub>; 0.2 ml (from a 1M stock solution) DTT; 5.0 ml (from a 1M stock solution)
- 30 HEPES; 0.1 ml TX-100; bring to 10 ml total volume with MilliQ H<sub>2</sub>O.

213

e. Lysis Buffer: 5.0 HEPES (from 1M stock solution.); 2.74 ml NaCl (from 5M stock solution); 10 ml glycerol; 1.0 ml TX-100; 0.4 ml EDTA (from a 100 mM stock solution); 1.0 ml PMSF (from a 100 mM stock solution); 0.1  
5 ml  $\text{Na}_3\text{VO}_4$  (from a 0.1 M stock solution); bring to 100 ml total volume with MilliQ  $\text{H}_2\text{O}$ .

f. ATP: Sigma Cat. # A-7699, make up 10 mM stock solution (5.51 mg/ml).

g TRIS-HCl: Fischer Cat. # BP 152-5, to 600 ml  
10 MilliQ  $\text{H}_2\text{O}$  add 121.14 g material, adjust pH to 7.5 with HCl, bring to 1 L total volume with MilliQ  $\text{H}_2\text{O}$ .

h. NaCl: Fischer Cat. # S271-10, Make up 5M stock solution with MilliQ  $\text{H}_2\text{O}$ .

i  $\text{Na}_3\text{VO}_4$ : Fischer Cat. # S454-50; to 80 ml MilliQ  
15  $\text{H}_2\text{O}$ , add 1.8 g material; adjust pH to 10.0 with HCl or NaOH; boil in a microwave; cool; check pH, repeat pH adjustment until pH remains stable after heating/cooling cycle; bring to 100 ml total volume with MilliQ  $\text{H}_2\text{O}$ ; make 1 ml aliquots and store at  $-80^\circ\text{C}$ .

20 j.  $\text{MgCl}_2$ : Fischer Cat. # M33-500, make up 1M stock solution with MilliQ  $\text{H}_2\text{O}$ .

k. HEPES: Fischer Cat. # BP 310-500; to 200 ml MilliQ  $\text{H}_2\text{O}$ , add 59.6 g material, adjust pH to 7.5, bring to 250 ml total volume with MilliQ  $\text{H}_2\text{O}$ , sterile filter (1M stock  
25 solution).

l. Albumin, Bovine (BSA), Sigma Cat. # A4503; to 150 ml MilliQ  $\text{H}_2\text{O}$  add 30 g material, bring 300 ml total volume with MilliQ  $\text{H}_2\text{O}$ , filter through  $0.22\ \mu\text{m}$  filter, store at  $4^\circ\text{C}$ .

m. TBST Buffer: To 900 ml  $\text{dH}_2\text{O}$  add 6.057 g TRIS and  
30 8.766 g NaCl; adjust pH to 7.2 with HCl, add 1.0 ml Triton-X100; bring to 1 L total volume with  $\text{dH}_2\text{O}$ .

n.  $\text{MnCl}_2$ : Fischer Cat. # M87-100, make up 1M stock solution with MilliQ  $\text{H}_2\text{O}$ .

o. DTT; Fischer Cat. # BP172-5.

p. TBS (TRIS Buffered Saline): to 900 ml MilliQ  $\text{H}_2\text{O}$   
5 add 6.057 g TRIS and 8.777 g NaCl; bring to 1 L total volume with MilliQ  $\text{H}_2\text{O}$ .

q Kinase Reaction Mixture: Amount per assay plate (100 wells): 1.0 ml Kinase Buffer, 200  $\mu\text{g}$  GST- $\square$ , bring to final volume of 8.0 ml with MilliQ  $\text{H}_2\text{O}$ .

10 2. Procedures:

a. Preparation of Lck coated ELISA plate.

1. Coat 2.0  $\mu\text{g}$ /well Sheep anti-mouse IgG in 100  $\mu\text{l}$  of pH 9.6 sodium carbonate buffer at 4°C overnight.

2. Wash well once with PBS.

15 3. Block plate with 0.15 ml of blocking Buffer for 30 min. at room temp.

4. Wash plate 5X with PBS.

5. Add 0.5  $\mu\text{g}$ /well of anti-lck (mab 3A5) in 0.1 ml PBS at room temperature for 1-2 hours.

20 6. Wash plate 5X with PBS.

7. Add 20  $\mu\text{g}$ /well of lck transformed yeast lysates diluted in Lysis Buffer (0.1 ml total volume per well). (Amount of lysate may vary between batches) Shake plate at 4°C overnight to prevent loss of activity.

25 b. Preparation of phosphotyrosine antibody-coated ELISA plate.

1. UB40 plate: 1.0  $\mu\text{g}$ /well UB40 in 100  $\mu\text{l}$  of PBS overnight at 4°C and block with 150  $\mu\text{l}$  of Blocking Buffer for at least 1 hour.

c. Kinase assay procedure.

1. Remove unbound proteins from step 1-7, above, and wash plates 5X with PBS.
2. Add 0.08 ml Kinase Reaction Mixture per well  
5 (containing 10  $\mu$ l of 10X Kinase Buffer and 2  $\mu$ g GST- $\square$  per well diluted with water).
3. Add 10  $\mu$ l of compound diluted in water containing 10% DMSO and pre-incubate for 15 minutes at room temperature.
- 10 4. Start kinase reaction by adding 10 $\mu$ l/well of 0.1 mM ATP in water (10  $\mu$ M ATP final).
5. Shake ELISA plate for 60 min. at room temperature.
6. Stop kinase reaction by adding 10  $\mu$ l of 0.5 M EDTA per well.
- 15 7. Transfer 90  $\mu$ l supernatant to a blocked 4G10 coated ELISA plate from section B, above.
8. Incubate while shaking for 30 min. at room temperature.
9. Wash plate 5X with TBST.
- 20 10. Incubate with Rabbit anti-GST antibody at 1:5000 dilution in 100  $\mu$ l TBST for 30 min. at room temperature.
11. Wash the wells 5X with TBST.
12. Incubate with Goat anti-Rabbit-IgG-HRP at 1:20,000 dilution in 100  $\mu$ l of TBST for 30 min. at room temperature.
- 25 13. Wash the wells 5X with TBST.
14. Develop with Turbo TMB.

i. Assay Measuring Phosphorylating Function Of Raf

The following assay reports the amount of RAF-catalyzed phosphorylation of its target protein MEK as well as MEK's  
30 target MAPK. The RAF gene sequence is described in Bonner

et al., 1985, Molec. Cell. Biol. 5: 1400-1407, and is readily accessible in multiple gene sequence data banks. Construction of the nucleic acid vector and cell lines utilized for this portion of the invention are fully described in Morrison et al., 1988, Proc. Natl. Acad. Sci. USA 85: 8855-8859.

#### Materials and Reagents

1. *Sf9* (*Spodoptera frugiperda*) cells; GIBCO-BRL, Gaithersburg, MD.
- 10 2. RIPA buffer: 20 mM Tris/HCl pH 7.4, 137 mM NaCl, 10% glycerol, 1 mM PMSF, 5 mg/L Aprotinin, 0.5% Triton X-100;
3. Thioredoxin-MEK fusion protein (T-MEK): T-MEK expression and purification by affinity chromatography were performed according to the manufacturer's procedures.
- 15 Catalog# K 350-01 and R 350-40, Invitrogen Corp., San Diego, CA
4. His-MAPK (ERK 2); His-tagged MAPK was expressed in XL1 Blue cells transformed with pUC18 vector encoding His-MAPK. His-MAPK was purified by Ni-affinity chromatography.
- 20 Cat# 27-4949-01, Pharmacia, Alameda, CA, as described herein.
5. Sheep anti mouse IgG: Jackson laboratories, West Grove, PA. Catalog, # 515-006-008, Lot# 28563
- 25 6. RAF-1 protein kinase specific antibody: URP2653 from UBI.
7. Coating buffer: PBS; phosphate buffered saline, GIBCO-BRL, Gaithersburg, MD
8. Wash buffer: TBST - 50 mM Tris/HCL pH 7.2, 150 mM NaCl, 0.1% Triton X-100
- 30 9. Block buffer: TBST, 0.1% ethanolamine pH 7.4

10. DMSO, Sigma, St. Louis, MO
11. Kinase buffer (KB): 20 mM HEPES/HCl pH 7.2, 150 mM NaCl, 0.1% Triton X-100, 1 mM PMSF, 5 mg/L Aprotinin, 75 mM sodium ortho vanadate, 0.5 mM DTT and 10 mM MgCl<sub>2</sub>.
- 5 12. ATP mix: 100 mM MgCl<sub>2</sub>, 300 mM ATP, 10 mCi <sup>33</sup>P ATP (Dupont-NEN)/mL.
- 13 Stop solution: 1% phosphoric acid; Fisher, Pittsburgh, PA.
14. Wallac Cellulose Phosphate Filter mats; Wallac,  
10 Turku, Finland.
15. Filter wash solution: 1% phosphoric acid, Fisher, Pittsburgh, PA.
16. Tomtec plate harvester, Wallac, Turku, Finland.
17. Wallac beta plate reader # 1205, Wallac, Turku,  
15 Finland.
18. NUNC 96-well V bottom polypropylene plates for compounds Applied Scientific Catalog # AS-72092.

#### Procedure

20 All of the following steps were conducted at room temperature unless specifically indicated.

1. ELISA plate coating: ELISA wells are coated with 100 ml of Sheep anti mouse affinity purified antiserum (1 mg/100 mL coating buffer) over night at 4°C. ELISA plates can be used for two weeks when stored at 4°C.
- 25 2. Invert the plate and remove liquid. Add 100 mL of blocking solution and incubate for 30 min.
3. Remove blocking solution and wash four times with wash buffer. Pat the plate on a paper towel to remove excess liquid.
- 30 4. Add 1 mg of antibody specific for RAF-1 to each well and incubate for 1 hour. Wash as described in step 3.

5. Thaw lysates from RAS/RAF infected Sf9 cells and dilute with TBST to 10 mg/100 mL. Add 10 mg of diluted lysate to the wells and incubate for 1 hour. Shake the plate during incubation. Negative controls receive no  
5 lysate. Lysates from RAS/RAF infected Sf9 insect cells are prepared after cells are infected with recombinant baculoviruses at a MOI of 5 for each virus, and harvested 48 hours later. The cells are washed once with PBS and lysed in RIPA buffer. Insoluble material is removed by  
10 centrifugation (5 min at 10 000 x g). Aliquots of lysates are frozen in dry ice/ethanol and stored at -80°C until use.

6. Remove non-bound material and wash as outlined above (step 3).

7. Add 2 mg of T-MEK and 2 mg of His-MAEPK per well  
15 and adjust the volume to 40 mL with kinase buffer. Methods for purifying T-MEK and MAPK from cell extracts are provided herein by example.

8. Pre-dilute compounds (stock solution 10 mg/mL DMSO) or extracts 20 fold in TBST plus 1% DMSO. Add 5 mL of  
20 the pre-diluted compounds/extracts to the wells described in step 6. Incubate for 20 min. Controls receive no drug.

9. Start the kinase reaction by addition of 5 mL ATP mix; Shake the plates on an ELISA plate shaker during incubation. 10. Stop the kinase reaction after 60 min by  
25 addition of 30 mL stop solution to each well.

11. Place the phosphocellulose mat and the ELISA plate in the Tomtec plate harvester. Harvest and wash the filter with the filter wash solution according to the manufacturers recommendation. Dry the filter mats. Seal the filter mats  
30 and place them in the holder. Insert the holder into radioactive detection apparatus and quantify the radioactive phosphorous on the filter mats.



Alternatively, 40 mL aliquots from individual wells of the assay plate can be transferred to the corresponding positions on the phosphocellulose filter mat. After air drying the filters, put the filters in a tray. Gently rock the tray, changing the wash solution at 15 min intervals for 1 hour. Air-dry the filter mats. Seal the filter mats and place them in a holder suitable for measuring the radioactive phosphorous in the samples. Insert the holder into a detection device and quantify the radioactive phosphorous on the filter mats.

j. CDK2/Cyclin A - Inhibition Assay

This assay analyzes the protein kinase activity of CDK2 in exogenous substrate.

Reagents:

15 A. Buffer A (80 mM Tris ( pH 7.2), 40 mM  $MgCl_2$ ): 4.84 G. Tris (F.W. =121.1 g/mol), 4.07 g.  $MgCl_2$  (F.W.=203.31 g/mol) dissolved in 500 ml  $H_2O$ . Adjust pH to 7.2 with HCl.

B. Histone H1 solution (0.45 mg/ml Histone H1 and 20 mM HEPES pH 7.2 (pH 7.4 is OK): 5 mg Histone H1 (Boehinger Mannheim) in 11.111 ml 20 mM HEPES pH 7.2 (477 mg HEPES (F.W.= 238.3 g/mol) dissolved in 100 ml dd $H_2O$ , stored in 1 ml aliquots at  $-80^\circ C$ .

C. ATP solution (60  $\mu M$  ATP, 300  $\mu g/ml$  BSA, 3 mM DTT): 120  $\mu l$  10 mM ATP, 600  $\mu l$  10 mg/ml BSA to 20 ml, stored in 1 ml aliquots at  $-80^\circ C$ .

D. CDK2 solution: cdk2/cyclin A in 10 mM HEPES pH 7.2, 25 mM NaCl, 0.5 mM DTT, 10% glycerol, stored in 9  $\mu l$  aliquots at  $-80^\circ C$ .

Description of Assay:

1. Prepare solutions of inhibitors at three times the desired final assay concentration in ddH<sub>2</sub>O/15% DMSO by volume.
- 5        2. Dispense 20  $\mu$ l of inhibitors to wells of polypropylene 96-well plates (or 20  $\mu$ l 15% DMSO for positive and negative controls).
3. Thaw Histone H1 solution (1 ml/plate), ATP solution (1 ml/plate plus 1 aliquot for negative control),  
10       and CDK2 solution (9 $\mu$ l/plate). Keep CDK2 on ice until use. Aliquot CDK2 solution appropriately to avoid repeated freeze-thaw cycles.
4. Dilute 9  $\mu$ l CDK2 solution into 2.1 ml Buffer A (per plate). Mix. Dispense 20  $\mu$ l into each well.
- 15       5. Mix 1 ml Histone H1 solution with 1 ml ATP solution (per plate) into a 10 ml screw cap tube. Add  $\gamma^{33}\text{P}$  ATP to a concentration of 0.15  $\mu\text{Ci}/20\mu\text{l}$  (0.15  $\mu\text{Ci}/\text{well}$  in assay). Mix carefully to avoid BSA frothing. Add 20  $\mu$ l to appropriate wells. Mix plates on plate shaker. For  
20       negative control, mix ATP solution with an equal amount of 20 mM HEPES pH 7.2 and add  $\gamma^{33}\text{P}$  ATP to a concentration of 0.15  $\mu\text{Ci}/20\mu\text{l}$  solution. Add 20  $\mu$ l to appropriate wells.
6. Let reactions proceed for 60 minutes.
7. Add 35  $\mu$ l 10% TCA to each well. Mix plates on  
25       plate shaker.
8. Spot 40  $\mu$ l of each sample onto P30 filter mat squares. Allow mats to dry (approx. 10-20 minutes).
- 9       Wash filter mats 4 X 10 minutes with 250 ml 1% phosphoric acid (10 ml phosphoric acid per liter ddH<sub>2</sub>O).
- 30       10. Count filter mats with beta plate reader.

## 2. Cellular/Biologic Assays

### Assay 1: PDGF-Induced BrdU Incorporation Assay

#### Materials and Reagents:

- (1) PDGF: human PDGF B/B; 1276-956, Boehringer  
5 Mannheim, Germany.
- (2) BrdU Labeling Reagent: 10 mM, in PBS (pH7.4),  
Cat. No. 1 647 229, Boehringer Mannheim, Germany.
- (3) FixDenat: fixation solution (ready to use), Cat.  
No. 1 647 229, Boehringer Mannheim, Germany.
- 10 (4) Anti-BrdU-POD: mouse monoclonal antibody  
conjugated with peroxidase, Cat. No. 1 647 229, Boehringer  
Mannheim, Germany.
- (5) TMB Substrate Solution: tetramethylbenzidine  
(TMB), ready to use, Cat. No. 1 647 229, Boehringer  
15 Mannheim, Germany.
- (6) PBS Washing Solution : 1X PBS, pH 7.4, made in  
house (Sugen, Inc., Redwood City, California).
- (7) Albumin, Bovine (BSA): fraction V powder; A-8551,  
Sigma Chemical Co., USA.
- 20 (8) 3T3 cell line genetically engineered to express  
human PDGF-R.

#### Protocol

- (1) Cells are seeded at 8000 cells/well in DMEM, 10%  
CS, 2mM Gln in a 96 well plate. Cells are incubated  
25 overnight at 37°C in 5% CO<sub>2</sub>.
- (2) After 24 hours, the cells are washed with PBS, and  
then are serum starved in serum free medium (0%CS DMEM with  
0.1% BSA) for 24 hours.
- (3) On day 3, ligand (PDGF, 3.8 nM, prepared in DMEM  
30 with 0.1% BSA) and test compounds are added to the cells

simultaneously. The negative control wells receive serum free DMEM with 0.1% BSA only; the positive control cells receive the ligand (PDGF) but no test compound. Test compounds are prepared in serum free DMEM with ligand in a  
5 96 well plate, and serially diluted for 7 test concentrations.

(4) After 20 hours of ligand activation, diluted BrdU labeling reagent (1:100 in DMEM, 0.1% BSA) is added and the cells are incubated with BrdU (final concentration=10  $\mu$ M)  
10 for 1.5 hours.

(5) After incubation with labeling reagent, the medium is removed by decanting and tapping the inverted plate on a paper towel. FixDenat solution is added (50  $\mu$ l/well) and the plates are incubated at room temperature for 45 minutes  
15 on a plate shaker.

(6) The FixDenat solution is thoroughly removed by decanting and tapping the inverted plate on a paper towel. Milk is added (5% dehydrated milk in PBS, 200  $\mu$ l/well) as a blocking solution and the plate is incubated for 30 minutes  
20 at room temperature on a plate shaker.

The blocking solution is removed by decanting and the wells are washed once with PBS. Anti-BrdU-POD solution (1:100 dilution in PBS, 1% BSA) is added (100  $\mu$ l/well) and the plate is incubated for 90 minutes at room temperature on  
25 a plate shaker.

(8) The antibody conjugate is thoroughly removed by decanting and rinsing the wells 5 times with PBS, and the plate is dried by inverting and tapping on a paper towel.

(9) TMB substrate solution is added (100  $\mu$ l/well) and  
30 incubated for 20 minutes at room temperature on a plate shaker until color development is sufficient for photometric detection.

223

(10) The absorbance of the samples are measured at 410 nm (in "dual wavelength" mode with a filter reading at 490 nm, as a reference wavelength) on a Dynatech ELISA plate reader.

5 Assay 2: EGF-Induced BrdU Incorporation Assay

Materials and Reagents

- (1) EGF: mouse EGF, 201; Toyobo, Co., Ltd. Japan.
- (2) BrdU Labeling Reagent: 10 mM, in PBS (pH7.4), Cat. No. 1 647 229, Boehringer Mannheim, Germany.
- 10 (3) FixDenat: fixation solution (ready to use), Cat. No. 1 647 229, Boehringer Mannheim, Germany.
- (4) Anti-BrdU-POD: mouse monoclonal antibody conjugated with peroxidase, Cat. No. 1 647 229, Boehringer Mannheim, Germany.
- 15 (5) TMB Substrate Solution: tetramethylbenzidine (TMB), ready to use, Cat. No. 1 647 229, Boehringer Mannheim, Germany.
- (6) PBS Washing Solution : 1X PBS, pH 7.4, made in house (Sugen, Inc., Redwood City, California).
- 20 (7) Albumin, Bovine (BSA): fraction V powder; A-8551, Sigma Chemical Co., USA.
- (8) 3T3 cell line genetically engineered to express human EGF-R.

Protocol

- 25 (1) Cells are seeded at 8000 cells/well in 10% CS, 2mM Gln in DMEM, in a 96 well plate. Cells are incubated overnight at 37°C in 5% CO<sub>2</sub>.
- (2) After 24 hours, the cells are washed with PBS, and then are serum starved in serum free medium (0% CS DMEM with
- 30 0.1% BSA) for 24 hours.

(3) On day 3, ligand (EGF, 2 nM, prepared in DMEM with 0.1% BSA) and test compounds are added to the cells simultaneously. The negative control wells receive serum free DMEM with 0.1% BSA only; the positive control cells receive the ligand (EGF) but no test compound. Test compounds are prepared in serum free DMEM with ligand in a 96 well plate, and serially diluted for 7 test concentrations.

(4) After 20 hours of ligand activation, diluted BrdU labeling reagent (1:100 in DMEM, 0.1% BSA) is added and the cells are incubated with BrdU (final concentration=10  $\mu$ M) for 1.5 hours.

(5) After incubation with labeling reagent, the medium is removed by decanting and tapping the inverted plate on a paper towel. FixDenat solution is added (50  $\mu$ l/well) and the plates are incubated at room temperature for 45 minutes on a plate shaker.

(6) The FixDenat solution is thoroughly removed by decanting and tapping the inverted plate on a paper towel. Milk is added (5% dehydrated milk in PBS, 200  $\mu$ l/well) as a blocking solution and the plate is incubated for 30 minutes at room temperature on a plate shaker.

(7) The blocking solution is removed by decanting and the wells are washed once with PBS. Anti-BrdU-POD solution (1:100 dilution in PBS, 1% BSA) is added (100  $\mu$ l/well) and the plate is incubated for 90 minutes at room temperature on a plate shaker.

(8) The antibody conjugate is thoroughly removed by decanting and rinsing the wells 5 times with PBS, and the plate is dried by inverting and tapping on a paper towel.

(9) TMB substrate solution is added (100  $\mu$ l/well) and incubated for 20 minutes at room temperature on a plate

shaker until color development is sufficient for photometric detection.

(10) The absorbance of the samples are measured at 410 nm (in "dual wavelength" mode with a filter reading at 490 nm, as a reference wavelength) on a Dynatech ELISA plate reader.

Assay 3: EGF-Induced Her2-Driven BrdU Incorporation

Materials and Reagents:

- (1) EGF: mouse EGF, 201; Toyobo, Co., Ltd. Japan
- 10 (2) BrdU Labeling Reagent: 10 mM, in PBS (pH7.4), Cat. No. 1 647 229, Boehringer Mannheim, Germany.
- (3) FixDenat: fixation solution (ready to use), Cat. No. 1 647 229, Boehringer Mannheim, Germany.
- (4) Anti-BrdU-POD: mouse monoclonal antibody  
15 conjugated with peroxidase, Cat. No. 1 647 229, Boehringer Mannheim, Germany.
- (5) TMB Substrate Solution: tetramethylbenzidine (TMB), ready to use, Cat. No. 1 647 229, Boehringer Mannheim, Germany.
- 20 (6) PBS Washing Solution: 1X PBS, pH 7.4, made in house.
- (7) Albumin, Bovine (BSA): fraction V powder; A-8551, Sigma Chemical Co., USA.
- (8) 3T3 cell line engineered to express a chimeric  
25 receptor having the extra-cellular domain of EGF-R and the intra-cellular domain of Her2.

Protocol:

- (1) Cells are seeded at 8000 cells/well in DMEM, 10% CS, 2mM Gln in a 96- well plate. Cells are incubated  
30 overnight at 37°C in 5% CO<sub>2</sub>.

(2) After 24 hours, the cells are washed with PBS, and then are serum starved in serum free medium (0%CS DMEM with 0.1% BSA) for 24 hours.

(3) On day 3, ligand (EGF=2 nM, prepared in DMEM with 0.1% BSA) and test compounds are added to the cells simultaneously. The negative control wells receive serum free DMEM with 0.1% BSA only; the positive control cells receive the ligand (EGF) but no test compound. Test compounds are prepared in serum free DMEM with ligand in a 96 well plate, and serially diluted for 7 test concentrations.

(4) After 20 hours of ligand activation, diluted BrdU labeling reagent (1:100 in DMEM, 0.1% BSA) is added and the cells are incubated with BrdU (final concentration = 10  $\mu$ M) for 1.5 hours.

(5) After incubation with labeling reagent, the medium is removed by decanting and tapping the inverted plate on a paper towel. FixDenat solution is added (50  $\mu$ l/well) and the plates are incubated at room temperature for 45 minutes on a plate shaker.

(6) The FixDenat solution is thoroughly removed by decanting and tapping the inverted plate on a paper towel. Milk is added (5% dehydrated milk in PBS, 200  $\mu$ l/well) as a blocking solution and the plate is incubated for 30 minutes at room temperature on a plate shaker.

(7) The blocking solution is removed by decanting and the wells are washed once with PBS. Anti-BrdU-POD solution (1:100 dilution in PBS, 1% BSA) is added (100  $\mu$ l/well) and the plate is incubated for 90 minutes at room temperature on a plate shaker.



(8) The antibody conjugate is thoroughly removed by decanting and rinsing the wells 5 times with PBS, and the plate is dried by inverting and tapping on a paper towel.

(9) TMB substrate solution is added (100 µl/well) and  
5 incubated for 20 minutes at room temperature on a plate shaker until color development is sufficient for photometric detection.

(10) The absorbance of the samples are measured at 410 nm (in "dual wavelength" mode with a filter reading at 490  
10 nm, as a reference wavelength) on a Dynatech ELISA plate reader.

#### Assay 4: IGF1-Induced BrdU Incorporation Assay

##### Materials and Reagents:

(1) IGF1 Ligand: human, recombinant; G511, Promega  
15 Corp., USA.

(2) BrdU Labeling Reagent: 10 mM, in PBS (pH7.4), Cat. No. 1 647 229, Boehringer Mannheim, Germany.

(3) FixDenat: fixation solution (ready to use), Cat. No. 1 647 229, Boehringer Mannheim, Germany.

(4) Anti-BrdU-POD: mouse monoclonal antibody  
20 conjugated with peroxidase, Cat. No. 1 647 229, Boehringer Mannheim, Germany.

(5) TMB Substrate Solution: tetramethylbenzidine (TMB), ready to use, Cat. No. 1 647 229, Boehringer  
25 Mannheim, Germany.

(6) PBS Washing Solution: 1X PBS, pH 7.4, made in house (Sugen, Inc., Redwood City, California).

(7) Albumin, Bovine (BSA): fraction V powder; A-8551, Sigma Chemical Co., USA.

(8) 3T3 cell line genetically engineered to express human IGF-1 receptor.

Protocol:

(1) Cells are seeded at 8000 cells/well in DMEM, 10% CS, 2mM Gln in a 96- well plate. Cells are incubated overnight at 37°C in 5% CO<sub>2</sub>.

(2) After 24 hours, the cells are washed with PBS, and then are serum starved in serum free medium (0%CS DMEM with 0.1% BSA) for 24 hours.

(3) On day 3, ligand (IGF1=3.3 nM, prepared in DMEM with 0.1% BSA) and test compounds are added to the cells simultaneously. The negative control wells receive serum free DMEM with 0.1% BSA only; the positive control cells receive the ligand (IGF1) but no test compound. Test compounds are prepared in serum free DMEM with ligand in a 96 well plate, and serially diluted for 7 test concentrations.

(4) After 16 hours of ligand activation, diluted BrdU labeling reagent (1:100 in DMEM, 0.1% BSA) is added and the cells are incubated with BrdU (final concentration=10 µM) for 1.5 hours.

(5) After incubation with labeling reagent, the medium is removed by decanting and tapping the inverted plate on a paper towel. FixDenat solution is added (50 µl/well) and the plates are incubated at room temperature for 45 minutes on a plate shaker.

(6) The FixDenat solution is thoroughly removed by decanting and tapping the inverted plate on a paper towel. Milk is added (5% dehydrated milk in PBS, 200 µl/well) as a blocking solution and the plate is incubated for 30 minutes at room temperature on a plate shaker.

(7) The blocking solution is removed by decanting and the wells are washed once with PBS. Anti-BrdU-POD solution (1:100 dilution in PBS, 1% BSA) is added (100 µl/well) and the plate is incubated for 90 minutes at room temperature on a plate shaker.

(8) The antibody conjugate is thoroughly removed by decanting and rinsing the wells 5 times with PBS, and the plate is dried by inverting and tapping on a paper towel.

(9) TMB substrate solution is added (100 µl/well) and incubated for 20 minutes at room temperature on a plate shaker until color development is sufficient for photometric detection.

(10) The absorbance of the samples are measured at 410 nm (in "dual wavelength" mode with a filter reading at 490 nm, as a reference wavelength) on a Dynatech ELISA plate reader.

g. HUV-EC-C Assay

The following protocol may also be used to measure a compound's activity against PDGF-R, FGF-R, VEGF, aFGF or Flk-1/KDR, all of which are naturally expressed by HUV-EC cells.

Day 0

1. Wash and trypsinize HUV-EC-C cells (human umbilical vein endothelial cells, (American Type Culture Collection; catalogue no. 1730 CRL). Wash with Dulbecco's phosphate-buffered saline (D-PBS; obtained from Gibco BRL; catalogue no. 14190-029) 2 times at about 1 ml/10 cm<sup>2</sup> of tissue culture flask. Trypsinize with 0.05% trypsin-EDTA in non-enzymatic cell dissociation solution (Sigma Chemical Company; catalogue no. C-1544). The 0.05% trypsin was made

by diluting 0.25% trypsin/1 mM EDTA (Gibco; catalogue no. 25200-049) in the cell dissociation solution. Trypsinize with about 1 ml/25-30 cm<sup>2</sup> of tissue culture flask for about 5 minutes at 37°C. After cells have detached from the flask,  
5 add an equal volume of assay medium and transfer to a 50 ml sterile centrifuge tube (Fisher Scientific; catalogue no. 05-539-6).

2. Wash the cells with about 35 ml assay medium in the 50 ml sterile centrifuge tube by adding the assay  
10 medium, centrifuge for 10 minutes at approximately 200 g, aspirate the supernatant, and resuspend with 35 ml D-PBS. Repeat the wash two more times with D-PBS, resuspend the cells in about 1 ml assay medium/15 cm<sup>2</sup> of tissue culture flask. Assay medium consists of F12K medium (Gibco BRL;  
15 catalogue no. 21127-014) + 0.5% heat-inactivated fetal bovine serum. Count the cells with a Coulter Counter<sup>□</sup> (Coulter Electronics, Inc.) and add assay medium to the cells to obtain a concentration of 0.8-1.0x10<sup>5</sup> cells/ml.

3. Add cells to 96-well flat-bottom plates at 100  
20 µl/well or 0.8-1.0x10<sup>4</sup> cells/well; incubate ~24h at 37°C, 5% CO<sub>2</sub>.

#### Day 1

1. Make up two-fold drug titrations in separate 96-well plates, generally 50 µM on down to 0 µM. Use the same  
25 assay medium as mentioned in day 0, step 2 above. Titrations are made by adding 90 µl/well of drug at 200 µM (4X the final well concentration) to the top well of a particular plate column. Since the stock drug concentration is usually 20 mM in DMSO, the 200 µM drug concentration  
30 contains 2% DMSO.

Therefore, diluent made up to 2% DMSO in assay medium (F12K + 0.5% fetal bovine serum) is used as diluent for the drug titrations in order to dilute the drug but keep the DMSO concentration constant. Add this diluent to the  
5 remaining wells in the column at 60  $\mu$ l/well. Take 60  $\mu$ l from the 120  $\mu$ l of 200  $\mu$ M drug dilution in the top well of the column and mix with the 60  $\mu$ l in the second well of the column. Take 60  $\mu$ l from this well and mix with the 60  $\mu$ l in the third well of the column, and so on until two-fold  
10 titrations are completed. When the next-to-the-last well is mixed, take 60  $\mu$ l of the 120  $\mu$ l in this well and discard it. Leave the last well with 60  $\mu$ l of DMSO/media diluent as a non-drug-containing control. Make 9 columns of titrated drug, enough for triplicate wells each for 1) VEGF (obtained  
15 from Pepro Tech Inc., catalogue no. 100-200, 2) endothelial cell growth factor (ECGF) (also known as acidic fibroblast growth factor, or aFGF) (obtained from Boehringer Mannheim Biochemica, catalogue no. 1439 600); or, 3) human PDGF B/B (1276-956, Boehringer Mannheim, Germany) and assay media  
20 control. ECGF comes as a preparation with sodium heparin.

2. Transfer 50  $\mu$ l/well of the drug dilutions to the 96-well assay plates containing the  $0.8-1.0 \times 10^4$  cells/100  $\mu$ l/well of the HUV-EC-C cells from day 0 and incubate ~2 h at 37°C, 5% CO<sub>2</sub>.

25 3. In triplicate, add 50  $\mu$ l/well of 80  $\mu$ g/ml VEGF, 20 ng/ml ECGF, or media control to each drug condition. As with the drugs, the growth factor concentrations are 4X the desired final concentration. Use the assay media from day 0 step 2 to make the concentrations of growth factors.  
30 Incubate approximately 24 hours at 37°C, 5% CO<sub>2</sub>. Each well will have 50  $\mu$ l drug dilution, 50  $\mu$ l growth factor or media,

and 100  $\mu$ l cells, = 200  $\mu$ l/well total. Thus the 4X concentrations of drugs and growth factors become 1X once everything has been added to the wells.

#### Day 2

- 5           1. Add  $^3\text{H}$ -thymidine (Amersham; catalogue no. TRK-686) at 1  $\mu\text{Ci/well}$  (10  $\mu\text{l/well}$  of 100  $\mu\text{Ci/ml}$  solution made up in RPMI media + 10% heat-inactivated fetal bovine serum) and incubate ~24 h at 37°C, 5%  $\text{CO}_2$ . Note:  $^3\text{H}$ -thymidine is made up in RPMI media because all of the other applications for  
10 which we use the  $^3\text{H}$ -thymidine involve experiments done in RPMI. The media difference at this step is probably not significant. RPMI was obtained from Gibco BRL, catalogue no. 11875-051.

#### Day 3

- 15           1. Freeze plates overnight at -20°C.

#### Day 4

1. Thaw plates and harvest with a 96-well plate harvester (Tomtec Harvester 96<sup>(R)</sup>) onto filter mats (Wallac; catalogue no. 1205-401); read counts on a Wallac Betaplate<sup>(TM)</sup>  
20 liquid scintillation counter.

### 3. In Vivo Animal Models

#### A. Xenograft Animal Models

- The ability of human tumors to grow as xenografts in athymic mice (e.g., Balb/c, nu/nu) provides a useful in vivo  
25 model for studying the biological response to therapies for human tumors. Since the first successful xenotransplantation of human tumors into athymic mice, (Rygaard and Povlsen, 1969, Acta Pathol. Microbial. Scand. 77:758-760),

many different human tumor cell lines (e.g., mammary, lung, genitourinary, gastro-intestinal, head and neck, glioblastoma, bone, and malignant melanomas) have been transplanted and successfully grown in nude mice. The following assays may be used to determine the level of activity, specificity and effect of the different compounds of the present invention. Three general types of assays are useful for evaluating compounds: cellular/catalytic, cellular/biological and in vivo. The object of the cellular/catalytic assays is to determine the effect of a compound on the ability of a TK to phosphorylate tyrosines on a known substrate in a cell. The object of the cellular/biological assays is to determine the effect of a compound on the biological response stimulated by a TK in a cell. The object of the in vivo assays is to determine the effect of a compound in an animal model of a particular disorder such as cancer.

Suitable cell lines for subcutaneous xenograft experiments include C6 cells (glioma, ATCC # CCL 107), A375 cells (melanoma, ATCC # CRL 1619), A431 cells (epidermoid carcinoma, ATCC # CRL 1555), Calu 6 cells (lung, ATCC # HTB 56), PC3 cells (prostate, ATCC # CRL 1435), SKOV3TP5 cells and NIH 3T3 fibroblasts genetically engineered to overexpress EGFR, PDGFR, IGF-1R or any other test kinase. The following protocol can be used to perform xenograft experiments:

Female athymic mice (BALB/c, nu/nu) are obtained from Simonsen Laboratories (Gilroy, CA). All animals are maintained under clean-room conditions in Micro-isolator cages with Alpha-dri bedding. They receive sterile rodent chow and water ad libitum.

Cell lines are grown in appropriate medium (for example, MEM, DMEM, Ham's F10, or Ham's F12 plus 5% - 10% fetal bovine serum (FBS) and 2 mM glutamine (GLN)). All cell culture media, glutamine, and fetal bovine serum are purchased from Gibco Life Technologies (Grand Island, NY) unless otherwise specified. All cells are grown in a humid atmosphere of 90-95% air and 5-10% CO<sub>2</sub> at 37°C. All cell lines are routinely subcultured twice a week and are negative for mycoplasma as determined by the Mycotect method (Gibco).

Cells are harvested at or near confluency with 0.05% Trypsin-EDTA and pelleted at 450 x g for 10 min. Pellets are resuspended in sterile PBS or media (without FBS) to a particular concentration and the cells are implanted into the hindflank of the mice (8 - 10 mice per group, 2 - 10 x 10<sup>6</sup> cells/animal). Tumor growth is measured over 3 to 6 weeks using venier calipers. Tumor volumes are calculated as a product of length x width x height unless otherwise indicated. P values are calculated using the Students t-test. Test compounds in 50 - 100 µL excipient (DMSO, or VPD:D5W) was delivered by IP injection at different concentrations generally starting at day one after implantation.

#### B. Tumor Invasion Model

The following tumor invasion model has been developed and maybe used for the evaluation of therapeutic value and efficacy of the compounds identified to selectively inhibit KDR/FLK-1 receptor.



### Procedure

8 week old nude mice (female) (Simonsen Inc.) were used as experimental animals. Implantation of tumor cells was performed in a laminar flow hood. For anesthesia, 5 Xylazine/Ketamine Cocktail (100 mg/kg ketamine and 5 mg/kg Xylazine) are administered intraperitoneally. A midline incision is done to expose the abdominal cavity (approximately 1.5 cm in length) to inject  $10^7$  tumor cells in a volume of 100  $\mu$ l medium. The cells are injected either into 10 the duodenal lobe of the pancreas or under the serosa of the colon. The peritoneum and muscles are closed with a 6-0 silk continuous suture and the skin was closed by using wound clips. Animals were observed daily.

### Analysis

15 After 2-6 weeks, depending on gross observations of the animals, the mice are sacrificed, and the local tumor metastases, to various organs (lung, liver, brain, stomach, spleen, heart, muscle) are excised and analyzed (measurements of tumor size, grade of invasion, immunochemistry, and 20 in situ hybridization).

### D. Measurement of Cell Toxicity

Therapeutic compounds should be more potent in inhibiting protein kinase activity than in exerting a cytotoxic effect. A measure of the effectiveness and cell 25 toxicity of a compound can be obtained by determining the therapeutic index:  $IC_{50}/LD_{50}$ .  $IC_{50}$ , the dose required to achieve 50% inhibition, can be measured using standard techniques such as those described herein.  $LD_{50}$ , the dosage which results in 50% toxicity, can also be measured by 30 standard techniques (Mossman, 1983, J. Immunol. Methods,

65:55-63), by measuring the amount of LDH released (Korzeniewski and Callewaert, 1983, J. Immunol. Methods, 64:313; Decker and Lohmann-Matthes, 1988, J. Immunol. Methods, 115:61), or by measuring the lethal dose in animal  
5 models. Compounds with a large therapeutic index are preferred. The therapeutic index should be greater than 2, preferably at least 10, more preferably at least 50.

#### Conclusion

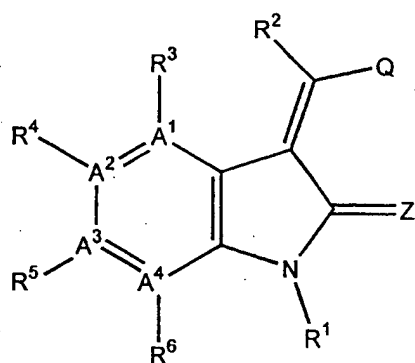
Thus, it will be appreciated that the compounds,  
10 methods and pharmacological compositions of the present invention are effective in modulating PK activity and therefore are expected to be effective as therapeutic agents against RTK, CTK-, and STK-related disorders.

Although certain embodiments and examples have been  
15 used to describe the present invention, it will be apparent to those skilled in the art that changes to the embodiments and examples shown may be made without departing from the scope and spirit of the invention.

Other embodiments are within the following claims.

Claims

1. A 2-indolinone having the chemical structure:



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and physiologically salts and prodrugs thereof wherein,

- 5     A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> and A<sup>4</sup> are independently selected from the group consisting of carbon and nitrogen, it being understood that the 9-member bicyclic ring formed is one known in the chemical arts; it further being understood that, when A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> or A<sup>4</sup> is nitrogen, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup>, respectively, does not  
10    exist;

- R<sup>1</sup> is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, trihalomethanecarbonyl, heteroalicyclic, hydroxy, alkoxy, carbonyl, C-carboxy, O-carboxy, C-amido, C-thioamido,  
15    guanyl,        guanadiny,        ureidyl,        sulfonyl        and trihalomethanesulfonyl;

      R<sup>2</sup> is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic and halo;

- 20     R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, alkyl, trihalomethyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic,

hydroxy, thiohydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, N-trihalomethanesulfonamido, carbonyl, aldehyde, trihalomethyl-carbonyl, C-carboxy, O-carboxy, cyano, nitro, halo, cyanato, isocyanato, thiocyanato, isothiocyanato, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, phosphonyl, guanyl, guanidiny, ureidyl, C-amido, N-amido, amino, quaternary ammonium,  $-NR^{18}R^{19}$ ,  $-W(CH_2)_mNR^{18}R^{19}$ ,  $-W(CH_2)_mC(=Y)T$ ,  $-N=CNR^{18}R^{19}$ ,  $-NHR^{20}$  and  $-(alk_1)_rM$ ;

$R^{18}$  and  $R^{19}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, acetyl, trihalomethylcarbonyl, C-carboxy, trihalomethane-sulfonyl, sulfonyl, C-peptidyl and, combined, a five-member or a six-member heteroalicyclic ring;

W is selected from the group consisting of nitrogen, oxygen and sulfur;

$(alk_1)$  is selected from the group consisting of  $-CRR'-$ ,  $-CR=CR'-$  and  $-C\equiv C-$ ;

R and R' are independently selected from the groups consisting of hydrogen, alkyl, cycloalkyl, aryl, alkoxy, thioalkoxy, aryloxy and halo;

r is 1 to 10, inclusive;

M is a polar group;

T is selected from the group consisting of hydroxy, alkoxy, aryloxy, amino, N-hydroxylamino, O-carboxy,  $-NR^{18}R^{19}$  and  $-N$ -peptidyl;

m is 0, 1, 2 or 3;

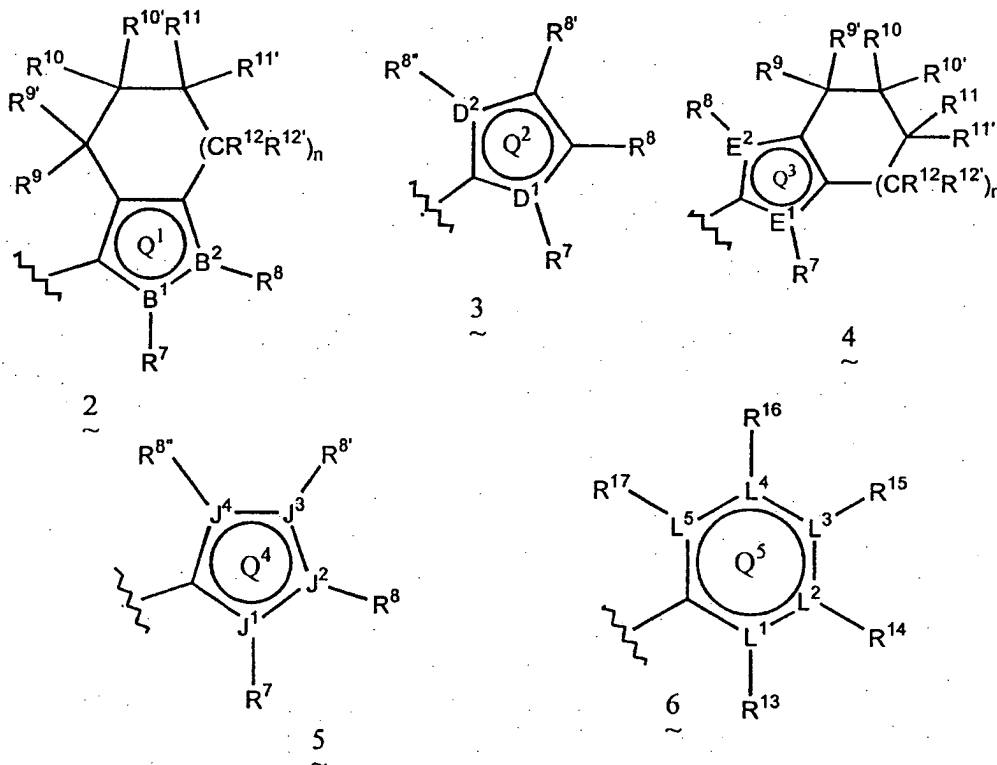
Y is selected from the group consisting of oxygen and sulfur;

$R^{20}$  is a polyhydroxyalkyl group;

$R^3$  and  $R^4$  or  $R^4$  and  $R^5$  or  $R^5$  and  $R^6$  may combine to form a cycloalkyl, aryl, heteroaryl, heteroalicyclic, methylenedioxy or an ethylenedioxy group;

Q is selected from the group consisting of:

5



$B^1$  and  $B^2$  are selected from the group consisting of carbon, nitrogen, oxygen and sulfur such that heteroaryl ring  $Q^1$  is one known in the chemical arts;

10  $D^1$  is selected from the group consisting of carbon and nitrogen;

$D^2$  is selected from the group consisting of nitrogen, oxygen and sulfur, it being understood that, when  $D^1$  is nitrogen and  $D^2$  is oxygen or sulfur,  $R^7$  or  $R^8$ , respectively, do not exist;

15

E<sup>1</sup> is selected from the group consisting of carbon and nitrogen;

E<sup>2</sup> is selected from the group consisting of nitrogen, oxygen and sulfur, it being understood that, when E<sup>1</sup> is nitrogen and E<sup>2</sup> is oxygen or sulfur, R<sup>8</sup> does not exist;

J<sup>1</sup> is selected from the group consisting of oxygen, nitrogen and sulfur;

J<sup>2</sup>, J<sup>3</sup> and J<sup>4</sup> are independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur such that the five-member heteroaryl ring Q<sup>4</sup> is one known in the chemical arts, it being further understood that, when J<sup>2</sup>, J<sup>3</sup> or J<sup>4</sup> is nitrogen, oxygen or sulfur, R<sup>8</sup>, R<sup>8'</sup> or R<sup>8''</sup>, respectively, do not exist, likewise when J<sup>1</sup> is oxygen or sulfur, R<sup>7</sup> does not exist;

L<sup>1</sup>, L<sup>2</sup>, L<sup>3</sup>, L<sup>4</sup> and L<sup>5</sup> are independently selected from the group consisting of carbon and nitrogen such that any 6-member nitrogen-containing heteroaryl ring Q<sup>5</sup> formed is one known in the chemical arts, it being further understood that, when L<sup>1</sup>, L<sup>2</sup>, L<sup>3</sup>, L<sup>4</sup> or L<sup>5</sup> is nitrogen R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> or R<sup>17</sup>, respectively, does not exist;

R<sup>7</sup>, R<sup>8</sup>, R<sup>8'</sup>, R<sup>8''</sup>, R<sup>9</sup>, R<sup>9'</sup>, R<sup>10</sup>, R<sup>10'</sup>, R<sup>11</sup>, R<sup>11'</sup>, R<sup>12</sup>, R<sup>12'</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are independently selected from the group consisting of hydrogen, alkyl, trihalomethyl, cycloalkyl, trihalomethylcarbonyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, alkoxy, aryloxy, thioalkoxy, thioaryloxy, heteroaryloxy, heteroalicycloxy, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, carbonyl, trihalomethylcarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, 1-piperazinyl, N-thio-carbamyl, phosphonyl, guanyl, guanidinyl, ureidyl, trihalo- methanesulfonyl, trihalomethanesulfonamido, amino,

-NR<sup>18</sup>R<sup>19</sup>, quaternary ammonium, -W(CH<sub>2</sub>)<sub>m</sub>NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>C(=Y)T, -N=CNR<sup>18</sup>R<sup>19</sup>, -NHR<sup>20</sup> and -(alk<sub>1</sub>)<sub>r</sub>M;

R<sup>7</sup> and R<sup>8</sup>, R<sup>8</sup> and R<sup>8'</sup> or R<sup>8'</sup> and R<sup>8''</sup>, combined, may form a five-member cycloalkyl, heteroaryl or heteroalicyclic ring or a six-member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring;

R<sup>7</sup> and R<sup>8</sup> and when R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> or R<sup>12</sup> is hydrogen, R<sup>9'</sup>, R<sup>10'</sup>, R<sup>11'</sup> or R<sup>12'</sup>, respectively, in addition to being selected from the above groups, may also be independently selected from the group consisting of hydroxy and thiohydroxy; and,

R<sup>9</sup> and R<sup>9'</sup>, R<sup>10</sup> and R<sup>10'</sup>, R<sup>11</sup> and R<sup>11'</sup>, R<sup>12</sup> and R<sup>12'</sup>, R<sup>21</sup> and R<sup>21'</sup>, R<sup>22</sup> and R<sup>22'</sup>, R<sup>24</sup> and R<sup>24'</sup> or R<sup>25</sup> and R<sup>25'</sup>, combined, may form a keto, five-member spirocycloalkyl, five-member spiroheteroalicyclic, six-member spirocycloalkyl or six-member spiroheteroalicyclic group.

2. The compound, salt or prodrug of claim 1 wherein, Z is oxygen.

3. The compound, salt or prodrug of claim 1 wherein, R<sup>1</sup> is hydrogen.

4. The compound, salt or prodrug of claim 1 wherein, R<sup>2</sup> is hydrogen.

5. The compound, salt or prodrug of claim 1 wherein, R<sup>7</sup> is hydrogen.

6. The compound, salt or prodrug of claim 1 wherein, A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> and A<sup>4</sup> are carbon.

7. The compound, salt or prodrug of claim 1 wherein,  
one of A<sup>1</sup>, A<sup>2</sup> or A<sup>3</sup> or A<sup>4</sup> is nitrogen, the rest being carbon.

8. The compound, salt or prodrug of claim 1 wherein,  
5 A<sup>2</sup> and A<sup>4</sup> are nitrogen while A<sup>1</sup> and A<sup>3</sup> are carbon.

9. The compound, salt or prodrug of claim 1 wherein,  
Z is oxygen;  
R<sup>1</sup>, R<sup>2</sup> and R<sup>7</sup> are hydrogen; and,  
10 A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> and A<sup>4</sup> are carbon.

10. The compound, salt or prodrug of claim 1 wherein,  
one of A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> or A<sup>4</sup> is nitrogen, the rest being  
carbon;  
15 Z is oxygen; and,  
R<sup>1</sup>, R<sup>2</sup> and R<sup>7</sup> are hydrogen.

11. The compound, salt or prodrug of claim 1 wherein,  
A<sup>1</sup> and A<sup>3</sup> are carbon;  
20 A<sup>2</sup> and A<sup>4</sup> are nitrogen;  
Z is oxygen; and,  
R<sup>1</sup>, R<sup>2</sup> and R<sup>7</sup> are hydrogen.

12. The compound salt or prodrug of claim 1, wherein,  
25 R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are independently selected from the  
group consisting of:  
hydrogen;  
unsubstituted lower alkyl;  
lower alkyl substituted with a group selected from the  
30 group consisting of:  
unsubstituted cycloalkyl;  
halo;



- hydroxy;  
unsubstituted lower alkoxy,  
C-carboxy;  
unsubstituted aryl;  
5 unsubstituted heteroaryl;  
unsubstituted heteroalicyclic;  
amino;  
quaternary ammonium; or,  
-NR<sup>18</sup>R<sup>19</sup>;  
10 unsubstituted cycloalkyl;  
hydroxy;  
unsubstituted lower alkyl alkoxy;  
lower alkyl alkoxy substituted with a group selected  
from the group consisting of:  
15 one or more halo groups;  
unsubstituted aryl; or,  
unsubstituted heteroaryl;  
trihalomethyl;  
halo;  
20 unsubstituted aryl;  
aryl substituted with one or more groups independently  
selected from the group consisting of:  
unsubstituted lower alkyl;  
lower alkyl substituted with one or more halo groups;  
25 trihalomethyl;  
halo;  
hydroxy;  
unsubstituted lower alkyl alkoxy;  
unsubstituted aryloxy;  
30 aryloxy substituted with one or more groups  
independently selected from the group consisting of:  
halo;

- unsubstituted lower alkyl;  
lower alkyl substituted with one or more halo groups;  
unsubstituted aryl;  
hydroxy;
- 5 unsubstituted lower alkyl alkoxy;  
amino; or,  
-NR<sup>18</sup>R<sup>19</sup>;  
amino;  
S-sulfonamido;
- 10 -NR<sup>18</sup>R<sup>19</sup>;  
unsubstituted aryloxy;  
unsubstituted heteroaryl;  
heteroaryl substituted with one or more groups  
independently selected from the group consisting of:
- 15 hydrogen;  
unsubstituted lower alkyl;  
lower alkyl substituted with one or more halo groups;  
trihalomethyl;  
halo;
- 20 hydroxy;  
unsubstituted lower alkyl alkoxy;  
unsubstituted aryloxy;  
amino;  
S-sulfonamido; or,
- 25 -NR<sup>18</sup>R<sup>19</sup>;  
unsubstituted heteroalicyclic;  
heteroalicyclic substituted with one or more groups  
independently selected from the group consisting of:
- 30 unsubstituted lower alkyl;  
lower alkyl substituted with one or more halo groups;  
unsubstituted lower alkyl alkoxy;  
hydroxy;

- amino;  
S-sulfonamido; or,  
-NR<sup>18</sup>R<sup>19</sup>;  
unsubstituted lower alkyl C-carboxy;  
5 carboxylic acid;  
unsubstituted lower alkyl carbonyl;  
aldehyde;  
unsubstituted aryl carbonyl;  
acetyl;  
10 S-sulfonamido;  
N-sulfonamido;  
amino; and,  
-NR<sup>18</sup>R<sup>19</sup>;  
R<sup>8</sup>, R<sup>8'</sup> and R<sup>8''</sup> are independently selected from the group  
15 consisting of hydrogen, unsubstituted lower alkyl, halo,  
cyano, nitro, C-carboxy, unsubstituted cycloalkyl, unsubsti-  
tuted aryl, unsubstituted heteroaryl, unsubstituted  
heteroalicyclic, trihalomethyl, unsubstituted lower alkenyl,  
unsubstituted lower alkynyl, hydroxy, unsubstituted lower  
20 alkyl alkoxy, unsubstituted aryloxy, sulfinyl, sulfonyl, S-  
sulfonamido, N-sulfonamido, carbonyl, C-carboxy, O-carboxy,  
cyano, nitro, halo, C-amido, N-amido, O-carbamyl, N-  
carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl,  
guanadiny, ureidyl and -NR<sup>18</sup>R<sup>19</sup>;  
25 R<sup>9</sup>, R<sup>9'</sup>, R<sup>10</sup>, R<sup>10'</sup>, R<sup>11</sup>, R<sup>11'</sup>, R<sup>12</sup>, R<sup>12'</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> and  
R<sup>17</sup> are independently selected from the group consisting of:  
hydrogen;  
unsubstituted lower alkyl;  
trihalomethyl  
30 unsubstituted cycloalkyl;  
trihalomethylcarbonyl;  
unsubstituted lower alkenyl;

- unsubstituted lower alkynyl;  
unsubstituted aryl;  
aryl substituted with one or more groups selected from  
the group consisting of:
- 5        unsubstituted lower alkyl;  
         unsubstituted lower alkyl alkoxy;  
         unsubstituted aryl;  
         unsubstituted aryloxy,  
         unsubstituted heteroaryl;
- 10       unsubstituted heteroalicyclic;  
         halo;  
         hydroxy;  
         amino;  
         -N<sup>18</sup>N<sup>19</sup>; or,
- 15       S-sulfonamido;  
         unsubstituted heteroaryl;  
         heteroaryl substituted with one or more groups selected  
from the group consisting of:
- 20       unsubstituted lower alkyl;  
         unsubstituted lower alkyl alkoxy,  
         unsubstituted aryl,  
         unsubstituted heteroaryl,  
         unsubstituted heteroalicyclic;  
         halo,
- 25       hydroxy,  
         amino;  
         -N<sup>18</sup>N<sup>19</sup>; or,  
         S-sulfonamido;  
         unsubstituted heteroalicyclic;
- 30       heteroalicyclic substituted with one or more groups  
selected from the group consisting of:  
         unsubstituted lower alkyl;

unsubstituted lower alkyl alkoxy;  
unsubstituted aryl;  
unsubstituted heteroaryl;  
halo;  
5 hydroxy;  
amino; or,  
S-sulfonamido;  
1-piperazinyl;  
unsubstituted lower alkoxy;  
10 unsubstituted aryloxy;  
sulfinyl;  
sulfonyl;  
S-sulfonamido;  
N-sulfonamido;  
15 carbonyl;  
C-carboxy;  
O-carboxy;  
C-amido;  
N-amido;  
20 cyano;  
nitro;  
halo;  
trihalomethanesulfonyl;  
trihalomethanesulfonamido;  
25 amino; or,  
-NR<sup>18</sup>R<sup>19</sup>; and,  
R<sup>18</sup>, R<sup>19</sup> and R" are selected from the group consisting of  
hydrogen and unsubstituted lower alkyl.

30 13. The compound, salt or prodrug of claim 12 wherein,  
A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> and A<sup>4</sup> are carbon;  
R<sup>1</sup>, R<sup>2</sup> and R<sup>7</sup> are hydrogen; and,

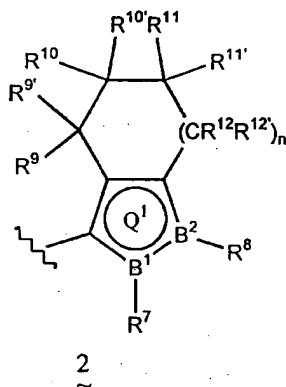
Z is oxygen.

14. The compound, salt or prodrug of claim 12 wherein,  
one of A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup> or A<sup>4</sup> is nitrogen and the rest are  
5 carbon;

R<sup>1</sup>, R<sup>2</sup> and R<sup>7</sup> are hydrogen; and,  
Z is oxygen.

15. The compound, salt or prodrug of claim 12 wherein,  
10 A<sup>1</sup> and A<sup>3</sup> are carbon;  
A<sup>2</sup> and A<sup>4</sup> are nitrogen;  
R<sup>1</sup>, R<sup>2</sup> and R<sup>7</sup> are hydrogen; and,  
Z is oxygen.

15 16. The compound, salt or prodrug of claim 13 wherein,  
Q is

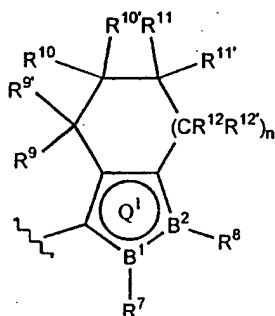


B<sup>1</sup> is nitrogen;  
20 B<sup>2</sup> is selected from the group consisting of sulfur and  
oxygen;

n is 0 or 1; and,

R<sup>9</sup>, R<sup>9'</sup>, R<sup>10</sup>, R<sup>10'</sup>, R<sup>11</sup>, R<sup>11'</sup>, R<sup>12</sup> and R<sup>12'</sup> are hydrogen.

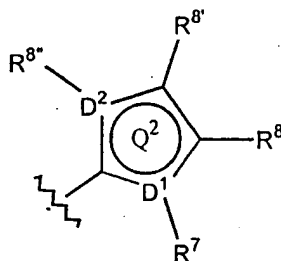
17. The compound, salt or prodrug of claim 13 wherein,  
Q is



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5      B¹ and B² are nitrogen;  
n is 0 or 1; and,  
R⁹, R⁹', R¹⁰, R¹⁰', R¹¹, R¹¹', R¹² and R¹²' are hydrogen.

18. The compound, salt or prodrug of claim 13 wherein,  
10      Q is



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one of R⁸ or R⁸' is selected from the group consisting of  
-NR¹⁸R¹⁹, -W(CH₂)ₘNR¹⁸R¹⁹, -W(CH₂)ₘC(=Y)T, -N=CNR¹⁸R¹⁹ and -  
NHR²⁰;

15      W and Y are independently selected from the group  
consisting of oxygen and sulfur;  
m is 1 or 2;

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T is selected from the group consistin of hydroxy, amino, N-hydroxylamino or N-peptidyl;

R<sup>18</sup> and R<sup>19</sup> are independently selected from the group consisting of hydrogen and unsubstituted lower alkyl; and,

5 R<sup>20</sup> is a lower polyhydroxyalkyl group.

19. The compound, salt or prodrug of claim 18 wherein,  
D<sup>1</sup> is nitrogen; and,  
D<sup>2</sup> is carbon.

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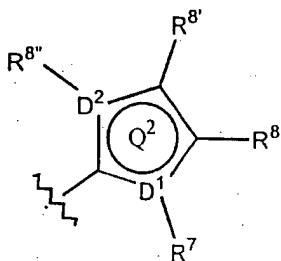
20. The compound, salt or prodrug of claim 18 wherein,  
D<sup>1</sup> is nitrogen; and,  
D<sup>2</sup> is sulfur.

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21. The compound, salt or prodrug of claim 18 wherein  
D<sup>1</sup> and D<sup>2</sup> are nitrogen.

22. The compound, salt or prodrug of claim 18 wherein,  
D<sup>1</sup> is selected from the group consisting of oxygen and  
20 sulfur; and,  
D<sup>2</sup> is carbon.

23. The compound, salt or prodrug of claim 13 wherein,  
Q is

3  
~

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D<sup>1</sup> is sulfur;

D<sup>2</sup> is carbon;

R<sup>8</sup> and R<sup>8'</sup>, combined, form an unsubstituted six-member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring;

5 one of R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> is selected from the group consisting of -NR<sup>18</sup>R<sup>19</sup>, -(CH<sub>2</sub>)<sub>m</sub>NR<sup>18</sup>R<sup>19</sup>, -W(CH<sub>2</sub>)<sub>m</sub>C(=Y)T, -N=CNR<sup>18</sup>R<sup>19</sup> and -NHR<sup>20</sup>;

W and Y are independently selected from the group consisting of oxygen and sulfur;

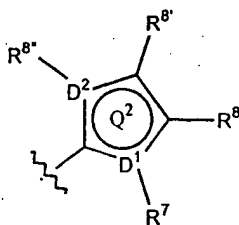
10 m is 1 or 2;

T is selected from the group consisting of hydroxy, amino, N-hydroxylamino and N-peptidyl;

R<sup>18</sup> and R<sup>19</sup> are independently selected from the group consisting of hydrogen and unsubstituted lower alkyl; and,

15 R<sup>20</sup> is a lower polyhydroxyalkyl group.

24. The compound, salt or prodrug of claim 14 wherein, Q is



3

20 D<sup>1</sup> is nitrogen;

D<sup>2</sup> is carbon;

R<sup>7</sup> hydrogen or unsubstituted lower alkyl;

R<sup>8</sup>, R<sup>8'</sup> and R<sup>8''</sup> are independently selected from the group consisting of:

25 hydrogen;

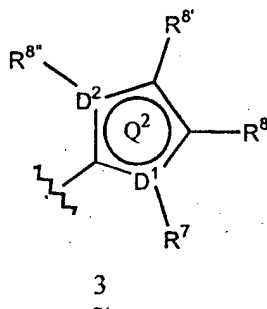
unsubstituted lower alkyl;

252

C-carboxy; or,  
combined,  $R^8$  and  $R^{8'}$  to form a six-member cycloalkyl  
ring;

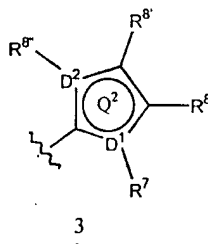
$R''$  is selected from the group consisting of hydrogen  
5 and unsubstituted lower alkyl.

25. The compound, salt or prodrug of claim 15 wherein,  
 $Q$  is



$D^1$  is nitrogen;  
10  $D^2$  is carbon;  
 $R^7$  hydrogen or unsubstituted lower alkyl;  
 $R^8$ ,  $R^{8'}$  and  $R^{8''}$  are independently selected from the group  
consisting of:  
hydrogen;  
15 unsubstituted lower alkyl;  
C-carboxy; and,  
 $R^8$  and  $R^{8'}$ , combined, to form a six-member cycloalkyl  
ring.

20 26. The compound, salt or prodrug of claim 14 wherein,  
 $Q$  is



253

D<sup>1</sup> is nitrogen;

D<sup>2</sup> is carbon; and,

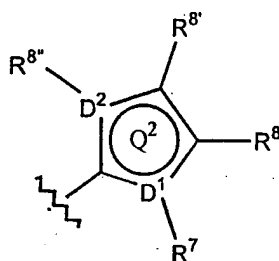
R<sup>8</sup> and R<sup>8''</sup> are selected from the group consisting of:

unsubstituted lower alkyl; or,

5 lower alkyl substituted with a carboxy group.

27. The compound, salt or prodrug of claim 15 wherein,

Q is



3  
~

10 D<sup>1</sup> is nitrogen;

D<sup>2</sup> is carbon; and,

R<sup>8</sup> and R<sup>8''</sup> are selected from the group consisting of:

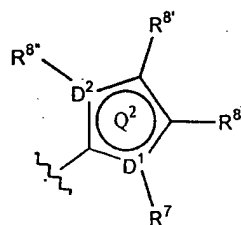
unsubstituted lower alkyl; or,

lower alkyl substituted with a carboxy group.

15

28. The compound, salt or prodrug of claim 14 wherein,

Q is



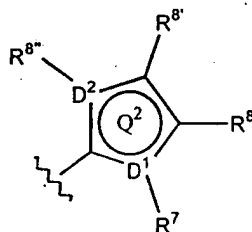
3  
~

D<sup>1</sup> is sulfur;

D<sup>2</sup> is carbon; and,

R<sup>8</sup>, R<sup>8'</sup> and R<sup>8''</sup> are independently selected from the group consisting of hydrogen, unsubstituted lower alkyl, lower alkyl substituted with a carboxy group, unsubstituted lower alkenyl, unsubstituted lower alkynyl, unsubstituted heteroaryl, unsubstituted aryloxy, unsubstituted lower alkyl thioalkoxy, halo, nitro, trihalomethylcarbonyl and an aryl or a heteroaryl ring formed by combining R<sup>8</sup> and R<sup>8'</sup>.

29. The compound salt or prodrug of claim 15 wherein, Q is



3  
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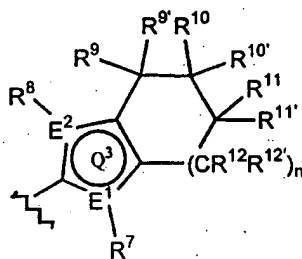
D<sup>1</sup> is sulfur;

D<sup>2</sup> is carbon; and,

R<sup>8</sup>, R<sup>8'</sup> and R<sup>8''</sup> are independently selected from the group consisting of hydrogen, unsubstituted lower alkyl, lower alkyl substituted with a carboxy group, unsubstituted lower alkenyl, unsubstituted lower alkynyl, unsubstituted heteroaryl, unsubstituted aryloxy, unsubstituted lower alkyl thioalkoxy, halo, nitro, trihalomethylcarbonyl and, combined, a six-member aryl or a 5 or 6-member heteroaryl ring.

30. The compound, salt or prodrug of claim 9 wherein, Q is

255



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E<sup>1</sup> is nitrogen;

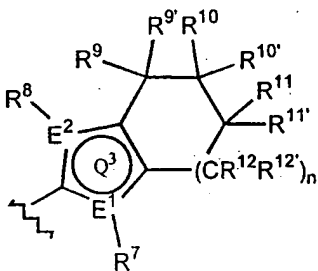
E<sup>2</sup> is carbon;

R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are independently selected from the  
 5 group consisting of hydrogen, unsubstituted lower alkyl, trihalomethyl, unsubstituted lower alkoxy, amino, halo, nitro, C-carboxy, C-amido, O-carbamyl and S-sulfonamido;

R<sup>8</sup> is selected from the group consisting of hydrogen, unsubstituted lower alkyl, unsubstituted lower cycloalkyl,  
 10 unsubstituted aryl, C-carboxy, cyano, unsubstituted alkenyl, hydroxy, unsubstituted lower alkoxy and unsubstituted aryloxy; and,

R<sup>9</sup>, R<sup>9'</sup>, R<sup>10</sup>, R<sup>10'</sup>, R<sup>11</sup>, R<sup>11'</sup>, R<sup>12</sup> and R<sup>12'</sup> are hydrogen.

15 31. The compound, salt or prodrug of claim 13 wherein,  
 Q is



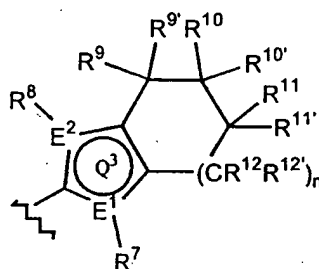
4

256

$E^1$  is selected from the group consisting of oxygen and sulfur; and,

$E^2$  is carbon.

- 5 32. The compound, salt or prodrug of claim 13, wherein, Q is

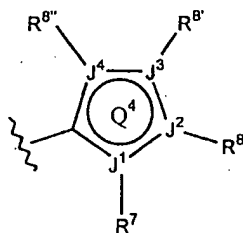


4

$E^1$  is nitrogen; and,

- 10  $E^2$  is selected from the group consisting of oxygen and sulfur.

33. The compound, salt or prodrug of claim 13, wherein, Q is



5

- 15 one of  $R^8$ ,  $R^{8'}$  or  $R^{8''}$  is an  $-(alk_1)_rM$  group;  
 $(alk_1)$  is  $CH_2$ ;  
 $r$  is 1 to 3, inclusive; and,

M is selected from the group consisting of hydroxy, amino, carboxy, unsubstituted morpholinyl, unsubstituted piperazinyl, unsubstituted tetrazolyl, N-carbamyl, O-carbamyl, S-sulfonamido, N-sulfonamido, sulfonyl, -S(O)<sub>2</sub>OH  
5 and phosphonyl;

the remaining two of R<sup>8</sup>, R<sup>8'</sup> and R<sup>8''</sup> are independently selected from the group consisting of:

hydrogen;  
unsubstituted lower alkyl;  
10 lower alkyl substituted with one or more groups selected from the group consisting of:  
halo;  
hydroxyl;  
unsubstituted lower alkoxy;  
15 amino;  
S-sulfonamido;  
-NR<sup>18</sup>R<sup>19</sup>; or,  
carboxy;  
unsubstituted lower alkoxy,  
20 lower alkoxy substituted with one or more halogens;  
unsubstituted aryl;  
aryl substituted with one or more groups selected from the group consisting of:  
unsubstituted lower alkyl;  
25 unsubstituted lower alkoxy;  
halo,  
trihalomethyl;  
amino;  
-NR<sup>18</sup>R<sup>19</sup>;  
30 hydroxy; or,  
S-sulfonamido;  
unsubstituted heteroaryl;

heteroaryl substituted with one or more groups selected from the group consisting of:

unsubstituted lower alkyl;

unsubstituted lower alkoxy;

5 halo,

trihalomethyl;

amino;

-NR<sup>18</sup>R<sup>19</sup>;

hydroxy; or,

10 S-sulfonamido;

unsubstituted heteroalicyclic;

heteroalicyclic substituted with one or more groups selected from the group consisting of:

unsubstituted lower alkyl;

15 halo;

hydroxy;

unsubstituted alkoxy;

amino; or,

-NR<sup>18</sup>R<sup>19</sup>;

20 halo;

cyano;

carboxy; and,

a six member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring formed by combining R<sup>8</sup> and R<sup>8'</sup> or R<sup>8'</sup> and R<sup>8''</sup>.

25

34. The compound, salt or prodrug of claim 33 wherein, any two of R<sup>8</sup>, R<sup>8'</sup> and R<sup>8''</sup> are (alk<sub>1</sub>)<sub>r</sub>M.

35. The compound, salt or prodrug of claim 33 wherein,  
30 J<sup>1</sup> is selected from the group consisting of nitrogen, oxygen and sulfur; and,

J<sup>2</sup>, J<sup>3</sup> and J<sup>4</sup> are carbon.



36. The compound, salt or prodrug of claim 34 wherein,  
 $J^1$  is selected from the group consisting of nitrogen,  
 oxygen and sulfur; and,

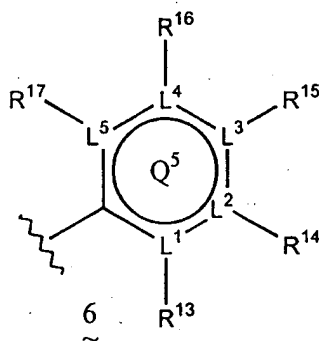
5  $J^2$ ,  $J^3$  and  $J^4$  are carbon.

37. The compound, salt or prodrug of claim 33 wherein,  
 $J^1$  and  $J^3$  are nitrogen; and,  
 $J^2$  and  $J^4$  are carbon.

10

38. The compound, salt or prodrug of claim 34 wherein,  
 $J^1$  and  $J^3$  are nitrogen; and,  
 $J^2$  and  $J^4$  are carbon.

15 39. The compound, salt or prodrug of claim 13 wherein,  
 $Q$  is



$L^1$ ,  $L^2$ ,  $L^3$ ,  $L^4$  and  $L^5$  are carbon;

one of  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  is 1-piperazinyl;

20  $R^{21}$ ,  $R^{21'}$ ,  $R^{22}$ ,  $R^{22'}$ ,  $R^{24}$ ,  $R^{24'}$ ,  $R^{25}$  and  $R^{25'}$  are hydrogen;

and,

the remaining of  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are  
 independently selected from the group consisting of  
 hydrogen, unsubstituted lower alkyl, trihalomethyl, halo,  
 25 hydroxy, unsubstituted lower alkoxy, unsubstituted aryloxy,

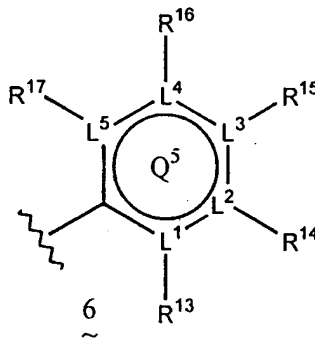
unsubstituted lower alkyl thioalkoxy or unsubstituted thioaryloxy.

40. The compound, salt of prodrug of claim 39 wherein,  
5  $R^{15}$  is 1-piperazinyl;

$R^{13}$ ,  $R^{14}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{21}$ ,  $R^{21'}$ ,  $R^{22}$ ,  $R^{22'}$ ,  $R^{24}$ ,  $R^{24'}$ ,  $R^{25}$  and  $R^{25'}$   
are independently selected from the group consisting of  
hydrogen, unsubstituted lower alkyl, trihalomethyl,  
unsubstituted lower alkoxy, halo, C-carboxy, O-carboxy,  
10 nitro, amino and S-sulfonamido; and,

$R^{23}$  is selected from the group consisting of hydrogen,  
unsubstituted lower alkyl and aldehyde.

41. The compound, salt or prodrug of claim 13 wherein,  
15 Q is; and,



$R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are independently selected from  
the group consisting of unsubstituted lower alkyl; lower  
20 alkyl substituted with one or more halo groups;  
unsubstituted aryl, unsubstituted heteroaryl, hydroxy,  
unsubstituted lower alkyl alkoxy, unsubstituted aryloxy,  
unsubstituted heteroaryloxy, halo, nitro, cyano, carbonyl,  
C-carboxy, O-carboxy, C-amido, N-amido, trihalomethyl, S-

sulfonamido, N-sulfonamido, aldehyde, carboxylic acid, amino and  $-NR^{18}R^{19}$ .

42. A method for the modulation of the catalytic activity of a protein kinase comprising contacting said protein kinase with said compound, salt or prodrug of any one of claims 1 through 41.

43. The method of claim 42 wherein said protein kinase comprises a protein tyrosine kinase.

44. The method of claim 43 wherein said protein tyrosine kinase comprises a receptor protein tyrosine kinase.

45. The method of claim 44 wherein said receptor protein tyrosine kinase is selected from the group consisting of EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFR $\alpha$ , PDGFR $\beta$ , CSF1R, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R and FGFR-4R.

46. The method of claim 43 wherein said protein tyrosine kinase comprises a non-receptor protein tyrosine kinase.

47. The method of claim 46 wherein said non-receptor protein tyrosine kinase is selected from the group consisting of Src, Frk, Btk, Csk, Abl, ZAP70, Fes/Eps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

48. The method of claim 42 wherein said protein kinase comprises a serine-threonine protein kinase.

49. The method of claim 48 wherein said serine-threonine protein kinase is selected from the group consisting of CDK2 and Raf.

5

50. A pharmacological composition of said compound, salt or prodrug of any one of claims 1 through 41.

51. A method for treating or preventing a protein kinase related disorder in an organism comprising administering a therapeutically effective amount of said pharmacological composition of claim 50 to said organism.

52. The method of claim 51 wherein said protein kinase related disorder comprises a receptor protein tyrosine kinase related disorder.

53. The method of claim 52 wherein said receptor tyrosine kinase related disorder comprises an EGFR related disorder.

54. The method of claim 53 wherein said EGFR related disorder is a cancer selected from the group consisting of squamous cell carcinoma, astrocytoma, glioblastoma, lung cancer, bladder cancer, head and neck cancer.

55. The method of claim 52 wherein said receptor protein tyrosine kinase related disorder comprises a PDGFR related disorder.

30

56. The method of claim 55 wherein said PDGFR related disorder is a cancer selected from the group consisting of

glioblastoma, melanoma, lung cancer, ovarian cancer or prostate cancer.

57. The method of claim 52 wherein said receptor  
5 protein tyrosine kinase related disorder comprises an IGFR related disorder.

58. The method of claim 57 wherein said IGFR related  
disorder is a cancer selected from the group consisting of  
10 breast cancer, small-cell lung cancer or glioma.

59. The method of claim 58 wherein said IGFR related disorder comprises diabetes.

15 60. The method of claim 52 wherein said protein tyrosine kinase related disorder comprises a flk related disorder.

61. The method of claim 60 wherein said flk related  
20 disorder is a cancer selected from the group consisting of breast cancer, ovarian cancer, lung carcinoma and glioblastoma.

62. The method of claim 51 wherein said protein kinase  
25 related disorder comprises a serine-threonine kinase related disorder.

63. The method of claim 62 wherein said serine-threonine kinase related disorder comprises an autoimmune  
30 disorder.

64. The method of claim 63 wherein said serine-threonine kinase related disorder comprises a hyper-proliferation disorder.

5        65. The method of claim 64 wherein said hyper-proliferation disorder is selected from the group consisting of restinosis, fibrosis, psoriasis, osteoarthritis and rheumatoid arthritis.

10       66. The method of claim 51 wherein said protein kinase related disorder comprises an inflammatory disorder.

67. The method of claim 51 wherein said protein kinase related disorder comprises angiogenesis.

15

68. The method of claim 51 wherein said organism is a mammal.

69. The method of claim 68 wherein said mammal is a  
20 human.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/09017

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) : CO7D 207/09, 209/42, 211/02, 307/02 US CL : 548/492, 400; 546/249; 549/483 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 548/492, 400; 546/249; 549/483  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched NONE  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,397,787 (BUZZETTI et al.) 03 March 1995, col.1, lines 1-68, col. 3, lines 20-68	1-12
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* *A* *E* *L* *O* *P*	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier document published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	*T* *X* *Y* *A* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
Date of the actual completion of the international search 17 JULY 1998		Date of mailing of the international search report 02 SEP 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer EBENEZER SACKNEY Telephone No. (703)-308-1235

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/09017

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☒ No protest accompanied the payment of additional search fees.



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/09017

### BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

**Group 1**

Compounds according to claim 1 where Q is an indole derivative.

**Group 2**

Compounds according to claim 1 where Q is a pyrrolidine.

**Group 3**

Compounds according to claim 1 where Q is a pyridine.

**Group 4**

Compounds according to claim 1 where Q is a furan.

**Group 5**

Compounds according to claim 1 where Q is a thiophene.

The inventions listed as Groups 1-5 do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: no special technical feature which makes a contribution over the prior art is found in all the structural possibilities depicted for the formula found in claim 1. The indole moiety of claim 1 is known in the art and, thus, does not make a contribution over the prior art. Therefore, any contribution over the prior art must come from the variable substituents and combinations thereof which are not found in every compound and are not known as equivalents in the art.

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